AUTOPSY STUDIES in SYPHILIS

A Monograph by

PAUL D. ROSAHN, M. D.

Supplement No. 21

to

The Journal of Venereal Disease Information

FEDERAL SECURITY AGENCY

U. S. Public Health Service

Venereal Disease Division

2

PRINTED IN U.S.A. CAT. NO. 24 161 BRO DART

AUTOPSY STUDIES IN SYPHILIS

A Monograph by

PAUL D. ROSAHN, M. D.

From the Department of Pathology, Yale University School of Medicine, and the Laboratories of the New Britain (Connecticut) General Hospital

Aided by a grant from the Venereal Disease Division of the United States Public Health Service.

FEDERAL SECURITY AGENCY

UNITED STATES PUBLIC HEALTH SERVICE

THOMAS PARRAN, *Surgeon General*

Editor: J. R. HELLER, JR., *Medical Director*
Chief, Venereal Disease Division

★

UNITED STATES GOVERNMENT PRINTING OFFICE, WASHINGTON : 1947

For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C.
Price 25 cents.

Dedicated to the Memory

of

WADE H. BROWN, M. D.

(1878-1942)

ACKNOWLEDGMENT

In April 1940, the writer solicited the financial support of the United States Public Health Service for a study of syphilis at autopsy to be based on the Yale post-mortem protocols. The proposal received the warm approval of Dr. R. A. Vonderlehr, then Chief of the Venereal Disease Division, and later of his successor, Dr. J. R. Heller, Jr., to both of whom grateful appreciation is extended. Their encouragement and critical judgment were of inestimable assistance in the development of the project.

By rare good fortune Dr. Bernard Black-Schaffer became associated with the investigation soon after its inception. He brought an active mind, great enthusiasm, and untiring effort to the task, until larger opportunities attracted him in 1942 to the Medical College of Virginia and more recently to Duke University. Dr. Black-Schaffer shared authorship in most of the publications arising from this study. It was largely due to his inexhaustible efforts that the laborious task of coding the autopsy protocols was completed.

The results of this investigation were published in several scattered reports under the general title "Studies in Syphilis." These papers are here collected under one cover. They originally appeared in the Archives of Internal Medicine, the American Journal of Syphilis, Gonorrhea and Venereal Diseases, the Yale Journal of Biology and Medicine, and the Journal of Venereal Disease Information. It is a pleasure to record thanks and appreciation to the editors and publishers of these journals for reprint permission.

The original texts are not here faithfully reproduced in meticulous detail. Rather, modifications, addenda, and deletions have been introduced wherever indicated. These, however, in no respect alter the basic tenets of the study as originally conceived and published.

November 1, 1946 PAUL D. ROSAHN, M. D.

CONTENTS

CHAPTER 1

INTRODUCTION [1]

Clinical investigations of the biology of syphilitic infection have been directed essentially to the problems of diagnosis, therapy and its complications. end results, and serology. By its very nature, the clinical approach has been practically limited to the study of the disease in the viable host, and as a result many tangential issues have received no more than cursory and scattered attention. It is apparent that the coordination and correlation of the clinical aspects of the disease with the observations at autopsy will throw light on many problems which are still in the penumbra of knowledge. How frequently do persons with clinically diagnosed syphilis present morphologic evidence of syphilis at autopsy? What is the relationship between clinical cure and morphologic lesions at death? How often does a person with clinically diagnosed syphilis die as a direct result of his disease, and how often is the disease a contributory or a noncontributory factor in causing death? Is the distribution of the causes of death among persons with syphilis, apart from this disease, any different from that of the nonsyphilitic population? Of corollary interest, does syphilis confer any susceptibility or resistance to other diseases? What, for instance, is the probability of death from cancer or from other morbid processes among syphilitic as compared with nonsyphilitic persons? Is there any correlation between serologic observations and morphologic evidence of syphilis at death? How does the longevity of the syphilitic person compare with that of the nonsyphilitic?

A stimulating paper by Moore (*1*) tersely summarized many unknowns in syphilology. "In spite of 400 years of study, we still do not know the actual importance of syphilis as a cause of death . . . To what extent . . . does death directly from syphilis masquerade under other diagnoses; or to what extent is syphilis an indirect cause of death from other conditions? . . .

"The modern necropsy studies of syphilitic patients, such as those of Warthin, provide no answers to these questions. Such studies, while revealing a very high incidence of lesions of syphilis, especially in aorta, heart, meninges, and testes, provide no correlation between the clinical status and the necropsy findings, no information as to cause of death, and no data as to the kind and amount of treatment, if any, given during life. What is clearly needed is a detailed study of both clinical and necropsy data in a very large series of patients, to provide information as to the frequency with which patients recognized as syphilitic during life, either on clinical or laboratory grounds, showed lesions of syphilis at necropsy and what these lesions, if any, were; the frequency with which patients adequately studied during life with no discoverable evidence of syphilis showed such evidence at necropsy; the relationship of clinically or pathologically recognized syphilis to the final illness and the direct or indirect cause of death; the relationship of necropsy evidence of syphilis to treatment during life; and a dozen similar factors as yet unknown."

These and other related problems form the background for a survey summarized in the following pages. The basis for this study consists of 5,300 autopsies performed in the Department of Pathology at the Yale University School of Medicine since 1917. Supplementary and complementary information has been derived from a review of the pertinent literature.

[1]This and the following chapter revise the article *Studies in Syphilis. I. Review of the Incidence of Syphilis in Autopsies on Adults,* by Paul D. Rosahn and Bernard Black-Schaffer, which was published in the *Archives of Internal Medicine,* vol. 72, p. 78, 1943.

CHAPTER 2

REVIEW OF THE INCIDENCE OF SYPHILIS IN AUTOPSIES ON ADULTS

The literature on the pathologic changes of syphilis contains no comparative or summated analysis of the isolated surveys of autopsy populations that have appeared from time to time. Many authors have directed their attention to specific types of syphilitic lesions, and as a result the scope of their studies has been limited to particular organ systems or to special tissue reactions. Comparatively few investigators have been concerned with the incidence of syphilis at autopsy in its broadest, all-inclusive aspects, and many of their studies have appeared in foreign publications not readily accessible in the United States.

It is here the principal purpose to collate and evaluate the available reports on the frequency of morphologically diagnosed syphilis in autopsy populations. The review is concerned with syphilis in its acquired form, and for convenience in analysis the autopsy populations have been limited to persons aged 20 and over. Wherever necessary, published reports have been recast to give the incidence of syphilis by decades beginning with the age of 20. This revision, however, in no way alters the factual data presented by the authors. It is admitted at the outset that there may be included a certain small number of syphilitic persons over 20 with congenital infections, but these are adequately counterbalanced by the exclusion of persons under 20, some of whom no doubt had acquired syphilis. At any rate the populations under consideration are large enough to reduce effectively any error introduced by taking the age of 20 as the arbitrary lower limit of acquired syphilis.

The Incidence of Syphilis at Autopsy

Table 1 presents a summary of available reports on the incidence of syphilitic lesions in autopsy populations. The data of this table are graphically depicted in chart 1. Four countries of continental Europe, one in Asia, one West Indian island, and the United States are represented. The frequency of syphilitic changes encountered at autopsy among persons over 20 years of age varies from a low of 2.6 percent to a high of 29.5 percent. The average for all of the 17 reports presented in the table is 8.8 percent. This average, however, gives equal weight to each of the reports regardless of the number of observations on which it was based. An alternative average value is one based on the entire summated autopsy population in the 17 reported series. Of a total of 146,761 persons, 7,993, or 5.45 percent, were observed to be syphilitic at autopsy.

Other reports on the incidence of syphilitic lesions at autopsy are available, but for the stated reasons they were not incorporated in table 1. Brines (*2*) studied 618 routine autopsies performed in 1934 at the City of Detroit Receiving Hospital, where 36 percent of the patients admitted were Negroes. He found 54 instances of gross and microscopic syphilis, an incidence of 8.7 percent, but failed to give the age and sex composition of the autopsy group. Turnbull (*3*) studied more than 7,000 necropsies performed in London between 1908 and 1913 and found that approximately 4 percent had lesions of acquired syphilis. Incomplete data prevent an exact computation of incidence. Pohlen (*4*) reviewed 8,182 autopsies performed in Magdeburg between 1928 and 1936. Of the sub-

TABLE 1.—*Incidence of syphilis at autopsy among persons aged 20 and over*

Author [1]	Country	Years	Number of autopsies	Persons with syphilis	
				Number	Percent
Herxheimer [2]	Germany	1906–1930	10,400	270	2.60
Bell (*10*)	U. S. A	1910–1937	19,785	601	3.04
Gürich [3]	Germany	1914–1924	23,179	806	3.48
Hansteen [4]	Norway	1907–1925	11,376	515	4.53
Teodori (*17*)	Italy	1918–1935	7,673	371	4.84
Frates (*18*)	Italy	1928–1933	8,217	418	5.09
Melchior (*19*)	Denmark	1914–1920	4,594	245	5.33
Langer[5]	Germany	1906–1925	23,015	1,268	5.51
Guldberg (*23*)	Norway	1896–1930	8,235	481	5.84
Symmers (*11*)	U. S. A	1906–1916	5,000	314	6.28
Nickel (*21*)	Germany	1907–1933	11,476	827	7.21
Ogden (*12*)	U. S. A	1931–1938	5,408	418	7.73
Ophüls (*7*)	U. S. A.	1900–1923	2,492	280	11.24
Koppisch (*9*)	Puerto Rico	1926–1938	665	75	11.28
Manohar (*8*)	India	1927–1934	2,721	431	15.84
Hala (*6*)	U. S. A	1922	850	179	21.06
Warthin (*5*)	U. S. A	1909–1929	1,675	494	29.49
Total (7 different countries)		1896–1938	146,761	7,993	5.45

[1] Figures in parentheses refer to bibliographic references.

[2] Herxheimer, J.: Syphilitische Veränderungen des Herzens und der Arterien, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol 16, pt 2

[3] Gürich: Ueber die syphilitischen Organveränderungen die unter dem Sektionsmaterial der Jahre, 1914–1924, angetroffen wurden, München. med Wchnschr 72:980, 1925

[4] Hansteen, cited by Guldberg (22).

[5] Langer, E.: Die Häufigkeit der luetischen Organveränderungen, insbesondere der Aortitis luetica, München med. Wchnschr, 73:1782, 1926.

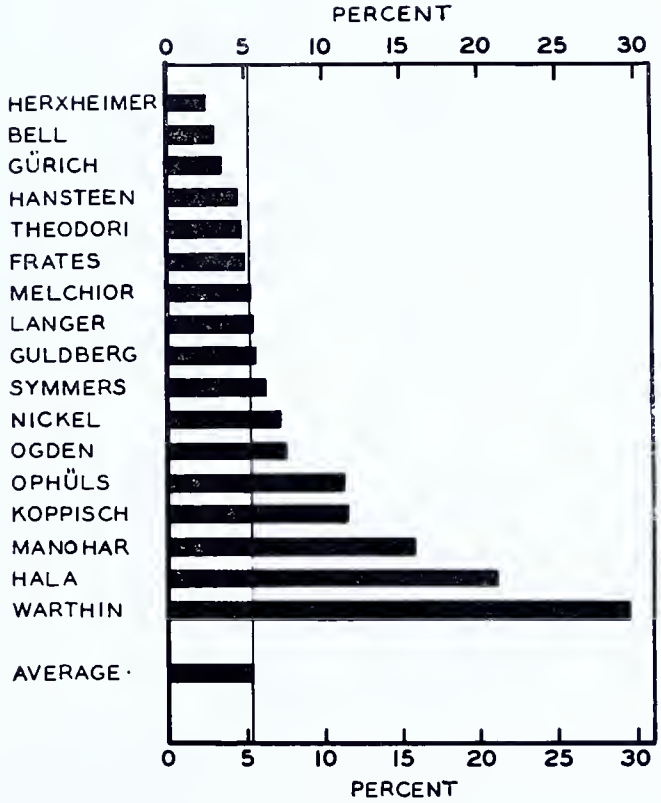

CHART 1.—The incidence of syphilis at autopsy among individuals over 20 years of age.

jects studied, 557, or 6.8 percent, had morphologic evidence of syphilis. This value includes both those with congenital and those with acquired lesions, who cannot be readily segregated on the basis of the data as given.

Twelve of the 17 reports listed in table 1 showed an incidence of syphilis of less than 8 percent, and only 5 authors gave an incidence higher than 11 percent. A comparison of individual results shows a striking variation between those of Warthin (*5*), Hala (*6*), Ophüls (*7*), Manohar (*8*), and Koppisch (*9*), on the one hand, and the remaining authors on the other. If we place the summated observations of these 5 authors in one classification and compare their results with those of the remaining authors, the difference is striking:

Authors	*Autopsies* *Number*	*Instances of syphilis* *Number*	*Percent*
Warthin, Hala, Ophüls, Manohar, and Koppisch	8,403	1,459	17.36
12 Others	138,358	6,534	4.72

It is, moreover, apparent that as regards reports emanating from the United States, there are two clear-cut and distinct schools of opinion. The first school, represented by Bell (*10*), Symmers (*11*), and Ogden (*12*), reported 1,333 instances of syphilis among 30,193 autopsies on persons aged 20 and over, a frequency of 4.4 percent. Warthin (*5*), Hala (*6*), and Ophüls (*7*) representing the second school, found 953 cases of syphilis in an autopsy population of 5,017, an incidence of 19 percent. The marked disparity between these two sets of results represents one of the outstanding problems of modern syphilology.

It is conceivable that the differences are real and characteristic of the different populations under investigation. On this basis syphilis was actually ten times as frequent in the population studied by Warthin as in that surveyed by Bell. If it is true that treatment effectively eliminates all morphologic traces of syphilis, the variable incidence might be explained by differences in the availability and intensity of syphilotherapy in the several communities forming the reservoirs for the different autopsy populations. Information on this point is outside the range of the present report, but other considerations suggest that the entire explanation does not lie in this direction. In the first place, the primary premise, that treatment effectively eradicates the morphologic changes of syphilis, is a problem yet to be settled. In the second place, even if this premise were accepted, the necessary conclusion that syphilis is treated over four times more effectively in New York, where Symmers found an incidence of 6.3 percent, than in Michigan, where Warthin reported a 29.5 percent frequency, would appear untenable.

Other factors, such as variability in economic status, in race, in age, and in sex distribution of the subjects comprising the different autopsy populations, are of importance, and these will be discussed in subsequent paragraphs. A critical analysis of the diagnostic criteria employed by the different authors may also throw some light on their widely divergent findings.

Analysis of Variables Contributing to Differences in Incidence

Race

It is well known that syphilis is much more frequent in the American Negro than in the white race. Keidel and Moore (*13*), among 5,000 patients admitted to the medical ward of Johns Hopkins Hospital, found positive Wassermann reactions of the blood in 7.6 percent of the white persons and in 22.9 percent of the Negroes. Among 4,000 discharged medical patients, syphilis was diagnosed in 9.7 percent of the white persons and in 25.4 percent of the Negroes.

An excellent opportunity to evaluate racial differences in the frequency of syphilitic infection was afforded by the data accumulated under the provisions of the Selective Training and Service Act of 1940. Vonderlehr and Usilton (*14*) analyzed the serologic blood test reports received through August 31, 1941, of 1,895,778 white and Negro men between ages 21 and 35. The rate of prevalence of syphilis, based on positive and doubtful blood tests, was 252.3 per thousand among Negro selectees, as contrasted to 17.4 per thousand among white selectees.

Other authors, notably Turner (*15*), and Paullin, Davison, and Wood (*16*), have re-

ported comparable results. However, it is not possible to explain the divergent results summarized in table 1 entirely on the basis of the racial composition of the different autopsy populations. All the European patients were adult Caucasians, and this is true also of Warthin's group. The population studied by Ophüls was composed of 91.3 percent white persons; no attempt was made to correlate race with morphologic changes, because of the small number of Negroes. Hala and Symmers made no mention of the racial composition of their groups. In Koppisch's series the incidence of syphilis among white persons was 8.6 percent, as contrasted to an incidence among mulattoes of 13.8 percent and among Negroes of 16.9 percent. These last two groups comprised 37.5 percent of the population and contributed 52 percent of the syphilitic subjects. The relatively high incidence of syphilis reported by Koppisch can thus be accounted for at least in part by the inclusion of a large number of mulattoes and Negroes, in whom the disease is more frequent than in the white race. Ogden's autopsy group consisted of 2,280 white persons, 89 of whom had syphilis, an incidence of 4 percent, and 3,128 Negroes, 329 of whom had anatomic syphilis, an incidence of 10.5 percent. Manohar's observations will receive more detailed discussion later.

The cardinal point with regard to race is that, although syphilis is demonstrably more frequent in the Negro than in the white person, the racial composition of the different populations is alone insufficient to explain the diverse results. Warthin, reporting the highest incidence, studied a population consisting solely of white persons.

Manohar requires special consideration because he was dealing with natives of India, a racial group not comparable to any investigated by the European and American authors. His series consists of two groups. The first was composed of 882 persons autopsied at the Grant Medical School, in Bombay. Syphilis was diagnosed at autopsy in 20.7 percent of these. The second comprised 1,839 persons autopsied by police surgeons, among whom 13.1 percent had lesions of syphilis. In the latter group only the principal cause of death was investigated, while the first was thoroughly studied by complete gross examinations. This author recorded the remarkable observation that 49 percent of the persons autopsied at the Medical School had syphilitic lesions of the heart, generally recognizable on gross examination. This observation, which is at complete variance with the entire literature, is explicable only on the basis of the author's diagnostic criteria. These, however, he fails to describe.

Social and Economic Status

It is difficult to evaluate the social and economic status of the autopsy populations studied by the various authors listed in table 1. Most of the reports are based on persons in the general category "city hospital patients." There were private patients in the series studied by Bell and in the populations analyzed by several of the German and Scandinavian authors. From this viewpoint alone, the 29.5-percent incidence of syphilis in Warthin's group of "private patients" is noteworthy.

Sex

Only five of the authors named in table 1 have published sufficient information to relate sex to acquired syphilis demonstrable by lesions at autopsy. Their reports are summarized in tables 2 and 3. Of 40,934 autopsied persons over 20, 62.3 percent were men and 37.7 percent were women. Among these, 1,763 had evidence of syphilitic infection, of whom 75.4 percent were men and 24.6 percent were women. Whereas approximately three-fifths of the autopsy population were men, men accounted for three-fourths of the cases of syphilis. Analysis by the chi-square test of homogeneity (table 3) indicates a statistically significant difference between these values. It can be concluded that a higher proportion of men and a lower proportion of women showed evidence of syphilis at autopsy than could be expected on the basis of the proportions of the sexes in the combined populations. Syphilis was diagnosed in 5.2 percent of the male population, a significantly higher percentage than that observed among women, i. e., 2.8 percent.

Each of the five authors presenting data on the sex incidence of syphilis at autopsy reported a frequency among males approximately twice that observed among females.

TABLE 2.—*Frequency of syphilitic lesions in men and in women as diagnosed at autopsy by five different investigators*

Author	Number of autopsies	Men, total		Women, total		Persons with syphilis			
						Men		Women	
		Number	Percent	Number	Percent	Number	Percent	Number	Percent
Bell	19,785	13,103	66.2	6,682	33.8	480	3.6	121	1.8
Frates	8,217	5,217	63.5	3,000	36.5	314	6.0	104	3.4
Koppisch	665	494	74.3	171	25.7	65	13.2	10	5.8
Melchior	4,594	2,482	54.0	2,112	46.0	171	6.9	74	3.5
Teodori	7,673	4,222	55.0	3,451	45.0	300	7.1	124	3.5
Total	40,934	25,518	62.3	15,416	37.7	1,330	5.2	433	2.8

Unfortunately, the reports of four authors, namely, Ophüls, Manohar, Hala, and Warthin, who found the highest incidence of syphilis, do not lend themselves to an analysis of the sex distribution either of their total autopsy population or of their syphilitic population. A critical evaluation of their material in the light of this general conclusion with regard to sex is therefore not feasible. It is, however, justifiable to conclude that the varied incidence of syphilis encountered by the different observers cannot be wholly the result of a preponderance of males in their autopsy populations.

TABLE 3.—*Frequency of syphilitic lesions in men and in women as diagnosed by five different investigators (observed and expected values)*

[Summarized from table 2]

Sex	Syphilitic		Nonsyphilitic		Total
	Observed	Expected	Observed	Expected	
Men	1,330	1,099	24,188	24,419	25,518
Women	433	664	14,983	14,752	15,416
Total	1,763	1,763	39,171	39,171	40,934

Age

The data presented by Teodori (*17*), Bell (*10*), Frates (*18*), Melchior (*19*), and Koppisch (*9*) are the only published reports sufficiently exhaustive to permit of a summated analysis of the incidence of syphilitic lesions at autopsy in relation to age at death. The findings of these five authors form the basis for the following discussion of age and syphilis in men at autopsy. The last author's data are not included in the consideration of age and syphilis in women because of the small number of women in his series. The data are presented in table 4 and in charts 2, 3, and 4. The figures were drawn on arithmetical probability paper and show the cumulative percentages by decades. A normal frequency distribution when charted on this type of paper is represented by a straight line. Deviation from a straight line is indicative of corresponding deviation from a normal distribution. The median is easily determined graphically by the intersection of the 50-percent ordinate with the frequency curve. The slope of the frequency line indicates the degree of variability of the data: the steeper the slope, the greater the variability (Schrek (*20*)).

The mean age (chart 4) of nonsyphilitic men over 20 was 54.70 ± 0.14 years, a value significantly higher than that found for nonsyphilitic women, 52.09 ± 0.23 years. The mean age of the men with syphilis was 52.53 ± 0.36 years, which is significantly

TABLE 4.—*Analysis of sex distribution of persons with and without syphilitic lesions at autopsy*

Age	Nonsyphilitic			Syphilitic		
	Number	Percent of total	Cumulative percent	Number	Percent of total	Cumulative percent
	MEN [1]					
20–29	2,229	9.2	9.2	22	1.7	1.7
30–39	2,356	9.7	18.9	173	13.4	15.1
40–49	4,459	18.4	37.4	358	27.7	42.8
50–59	5,373	22.2	59.6	381	29.5	72.3
60–69	5,384	22.3	81.9	272	21.1	93.3
70+	4,391	18.2	100.0	86	6.7	100.0
Total	24,192	100.0	.....	1,292	100.0	.....
	WOMEN [2]					
20–29	2,191	14.8	14.8	21	5.3	5.3
30–39	2,297	15.5	30.2	62	15.5	20.8
40–49	2,384	16.1	46.3	95	23.8	44.5
50–59	2,383	16.1	62.3	106	26.5	71.0
60–69	2,716	18.3	80.6	80	20.0	91.0
70+	2,874	19.4	100.0	36	9.0	100.0
Total	14,845	100.0	.....	400	100.0	.....

[1] The data are based on the reports of Bell, Frates, Koppisch, Melchior, and Teodori.

[2] The data are based on the reports of Bell, Frates, Melchior and Teodori.

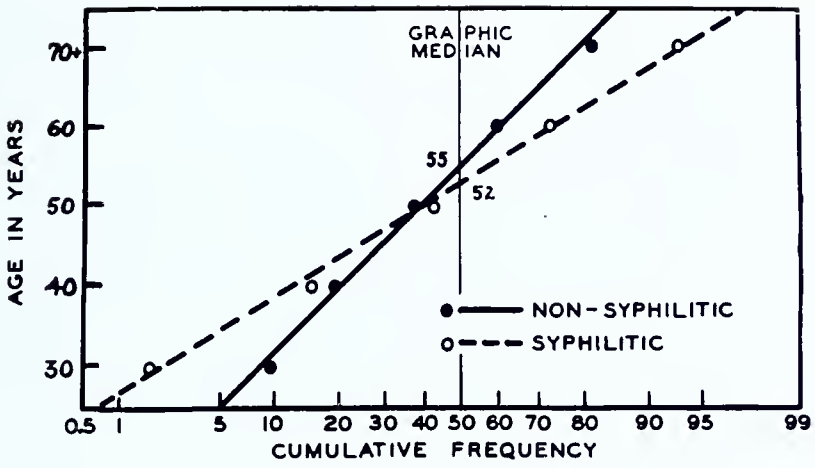

CHART 2.—Age of males with and without syphilitic lesions at autopsy.

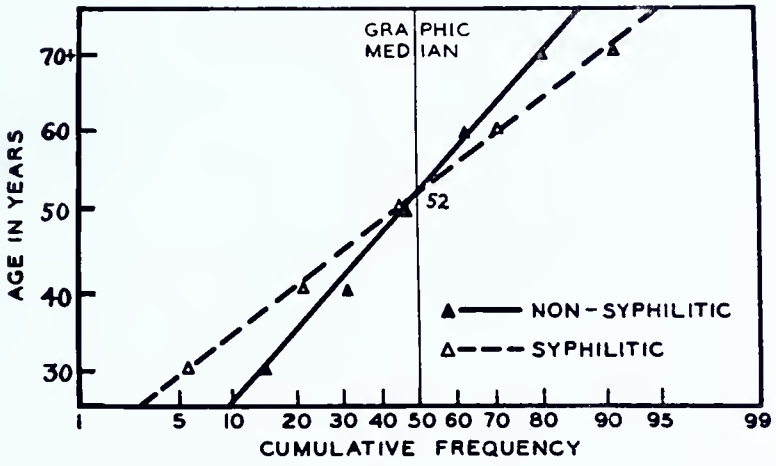

CHART 3.—Age of females with and without syphilitic lesions at autopsy.

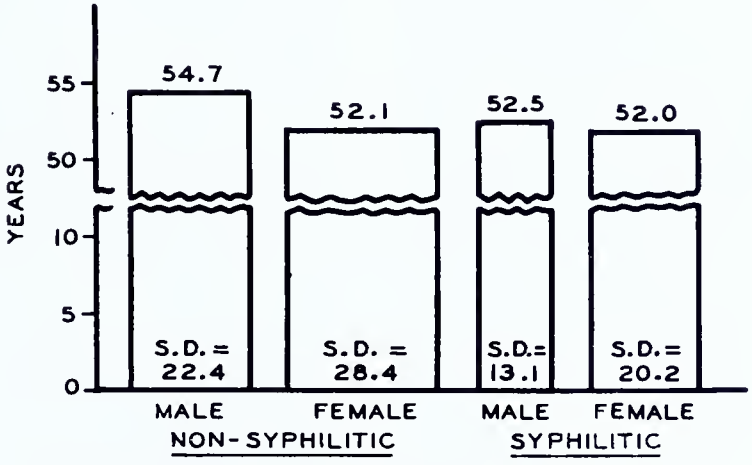

CHART 4.—Mean age and standard deviation of male and female individuals with and without lesions of syphilis at autopsy.

lower than that of the nonsyphilitic men. In contrast to this finding, the mean age of syphilitic women was 51.95 ± 1.01 years, actually no different from the mean value for the nonsyphilitic women. In these cumulative observations it appears that the average span of life of the syphilitic man was shortened by about 2 years, as compared with that of the nonsyphilitic man, although the woman with syphilis had an average duration of life no shorter than her nonsyphilitic sister. Differences in sex apparently exerted no significant influence on the average age at death of the syphilitic person, since both men and women with syphilis had a mean age of about 52 years.

Great care must be exercised in drawing conclusions from the mean age at death, because such values are easily affected by variations in the age distribution of different groups. For this reason the analysis shown in table 4 and charts 2 and 3 is presented. About 9 percent of the deaths in the nonsyphilitic male population over 20 years of age occurred during the third decade of life, as compared with less than 2 percent of the deaths among syphilitic men. Approximately 50 percent of the deaths in the nonsyphilitic group occurred between 30 and 59 years of age, while 70 percent of the syphilitic deaths took place in this age class. Finally, about 20 percent of the nonsyphilitic men survived beyond the age of 70, in contrast to less than 7 percent of those with syphilis.

A similar analysis of the data for women gives essentially similar results. About 15 percent of the deaths among nonsyphilitic women took place in the third decade of life, as compared with only 5 percent of the syphilitic deaths. Approximately half of the nonsyphilitic women died between 30 and 60 years of age, as compared with two-thirds of the syphilitic women. Moreover, about 20 percent of the nonsyphilitic women survived beyond the age of 70, in contrast to only 9 percent of the syphilitic women.

It is not our intent that these curves be interpreted as being typical of syphilis in this country. A composite curve was drawn instead of individual curves for each author in order to smooth the irregularities that would appear in the limited observations in the individual reports. These composite curves should be compared with each other as regards syphilitic and nonsyphilitic persons. From this viewpoint, and in the combined experience of the authors cited, the syphilitic man living into the forties and the syphilitic woman living into the fifties had a shorter life span than their nonsyphilitic brother and sister. It should be noted that each of the curves in charts 2 and 3 is represented by a straight line, indicating a normal frequency distribution. In chapter 5 these findings will be compared with those of the Yale experience, and the close parallelism between the two series will be shown.

One other observation with regard to age is of significance. This refers to the degree of variability of the frequency distributions for the syphilitic and nonsyphilitic men and women. In charts 2 and 3 the slope of the curve indicates variability; the steeper the slope the greater the variability. In chart 4 variability is proportional to the width of the bars. In both sexes the age distribution of the syphilitic group is less variable than that of the nonsyphilitic group, and this difference is highly significant. (The standard deviation equals 22.4 ± 0.10 for nonsyphilitic men and 13.07 ± 0.27 for syphilitic men, the difference being 9.33 ± 0.27, and t,35. The standard deviation equals 28.4 ± 0.16 for nonsyphilitic women, and 20.2 ± 0.23 for syphilitic women, the difference being 8.2 ± 0.28, and t,30.) The extremes of age between 20 and 70 are lopped off in the syphilitic groups as compared with the nonsyphilitic. Fewer young and fewer old subjects are found in the syphilitic than in the nonsyphilitic population.

The incidence of syphilis diagnosed at autopsy in relation to age and sex is shown in table 5. The highest incidence of syphilis occurred among men in the fifth decade and among women in the sixth decade, but in each decade syphilis was more frequent among men than among women. A possible but completely improbable explanation for the high incidence of syphilis in Warthin's, Hala's, and Ophüls' populations is here indicated. If their autopsy populations were composed entirely of Negro men aged 40 to 50, a plausible explanation for the high incidence of syphilis which they reported might be offered. There is internal evidence in their

publications, however, to discredit this hypothesis, and other explanations must therefore be sought.

TABLE 5.—*Incidence of syphilitic lesions at autopsy in men and in women according to age, by decades*

[Summated from reports of Bell, Frates, Koppisch, Melchior and Teodori]

Age	Total number		Syphilitic persons			
			Number		Percent	
	Men	Women	Men	Women	Men	Women
20–29.....	2,251	2,212	22	21	0.98	0.94
30–39.....	2,529	2,359	173	62	6.84	2.62
40–49.....	4,817	2,479	358	95	7.43	3.83
50–59.....	5,754	2,489	381	106	6.62	4.26
60–69.....	5,656	2,796	272	80	4.80	2.86
70+.....	4,477	2,910	86	36	1.92	1.24
Total..	25,484	15,245	1,292	400	5.07	2.62

Diagnostic Criteria

It is generally recognized that the criteria for the pathologic diagnosis of syphilis are not definitive. Before the advent of Warthin's *The New Pathology of Syphilis* a relative uniformity of criteria did not exist. These criteria were and still are to be found in the standard textbooks here and abroad. Outside of the United States and Canada, Warthin's influence has failed to make the impression which, on this continent at any rate, has resulted in the broadening of the pathologic concept of syphilis. This influence is more readily appreciated when the reports on lesions of individual organs, such as the stomach, testicle, kidney, liver, and adrenal glands, are considered than when the more general reports, such as those of table 1, are reviewed. It must, however, be stated that before Warthin's publications appeared, the specific nature of the syphilitic lesion was the subject of much controversy and in fact was the very basis which made Warthin's interpretation possible.

Because of the paucity of comparable anatomic studies, and the total lack of uniformity of criteria, the entire subject of the pathology of syphilis is a maze in which both the expert and the not-so-expert are frequently lost. When the incidence of syphilis of the liver in comparable populations ranges from 3.3 percent to 33.4 percent and when one author designates all hepatic syphilis as hepar lobatum, while another diagnoses only 33 percent as such, it is obvious that complete confusion in terminology and interpretation of lesions exists. It thus becomes apparent that of primary importance in an evaluation of statistics of this type are the criteria followed by the different observers. Here one finds sufficient variability to account in large part for the divergent results.

Warthin (*5*) stated: "The pathologic diagnosis of syphilis is essentially microscopic. Only in a relatively small number of cases are the gross lesions . . . typical enough to be recognized by the naked eye. A negative diagnosis of syphilis cannot be given with any certainty without a routine microscopic examination of all organs and tissues, but particularly of the left ventricular wall, the aorta, both its arch and abdominal portion, the testes, pancreas and adrenals . . .

"The new pathology of syphilis is based upon the demonstration that the essential tissue lesion of either late or latent syphilis is an irritative or inflammatory process, usually mild in degree, characterized by lymphocytic and plasma cell infiltrations in the stroma particularly about the blood vessels and lymphatics, slight tissue proliferation, eventually fibrosis, and atrophy or degeneration of the parenchyma."

This concept is in direct contrast to that of Nickel (*21*), who is representative of many of the authors listed in table 1. Nickel's criteria may be freely translated as follows: "Only definite anatomic syphilis, i. e., syphilitic vascular disease, syphilis of the central nervous system, syphilis of the bone, gumma, and interstitial hepatitis of the newborn, was included. Presumptive evidence of syphilis was not considered, i. e., orchitis fibrosa, cicatricial atrophy of the tongue, and so-called syphilitic cirrhosis, nor was a positive Wassermann reaction." Nickel specifically disregarded orchitis fibrosa, lingua glabia, and so-called syphilitic cirrhosis of the liver, nor did he mention changes in the pancreas and adrenals, as did Warthin. The latter also emphasized testicular fibrosis, and, in fact, Weller (*22*), who was for many years associated with Warthin, made the following statement: "In our opinion, testicular lesions rank second only to those of the aorta as to value in recognition of latent (nongummatous) visceral syphilis." The contrast between Warthin and Nickel is readily apparent and

is so sharply drawn that their conclusions cannot be fairly compared.

Symmers employed essentially the same criteria as Nickel but differed from him in the interpretation of specific lesions. For example, Symmers found that 33.4 percent of his syphilitic subjects presented hepatic syphilis of both the hepar lobatum type and the cirrhotic form, while Nickel specifically excluded from his series subjects with so-called syphilitic cirrhosis. Moreover, Symmers included subjects with the "presumptive changes of syphilis," such as orchitis fibrosa and lingua glabia, in his series. In spite of this, it is noteworthy that there is no significant difference between the 7-percent incidence reported by Nickel and the 6 percent observed by Symmers.

Hala, apparently a disciple of Warthin, accepted as syphilitic any subject to whom two of the following criteria applied: (1) a clinical history of antecedent infection or clinical evidence of existing syphilis, (2) a positive Wassermann reaction, (3) the observation of typical gross lesions at autopsy, and (4) histologic evidence of syphilis.

It is evident that the first two criteria are not anatomic, and since the number of subjects admitted to the series on this basis is not stated, the comparative value of the entire work is placed in jeopardy. Moreover, the freedom which the four criteria give to the author is evidenced by the statement that "subpleural aggregations of small round cells (miliary gummata?)" were noted in a considerable number of persons with syphilis, all of whom had pulmonary tuberculosis and the large majority of whom died of tuberculosis.

Frates included not only persons with anatomic lesions but also those with a positive Wassermann reaction or a clinical history of infection. However, these two groups are so well differentiated that it was possible to recalculate the author's findings and incorporate in table 1 only those cases in which there were definite anatomic lesions of syphilis.

Although Ophüls did not enumerate criteria in a formal statement, one may deduce them from his paper. For example, he included a subject with "myocardial syphilis on the basis of clinical history and course." He included another with chronic diffuse interstitial inflammation of pulmonary tissue with cor pulmonale, designated as syphilitic. Twenty percent of Ophüls' syphilitic patients had syphilitic hepatic disease, in contrast to Warthin's 30 percent and Nickel's 4.23 percent. Ophüls also included patients with orchitis fibrosa but added, "They may be syphilitic." The remainder of the authors followed in general the criteria described by Nickel.

The reports show considerable variation with respect to the routine use of microscopic examination of tissues, or of gross examination alone, in the anatomic diagnosis of syphilis. There is, however, compelling evidence that this variation is less important in accounting for the difference in frequency rates than is the variability in diagnostic criteria. Among authors relying entirely or almost entirely on gross examination in reaching a diagnosis of syphilis are Teodori, Frates, Symmers, Manohar, and Ophüls. The first three reported a frequency of 4.8 percent, 5.1 percent, and 6.3 percent, respectively. These are all comparable results. The last two authors recorded rates two and three times as great, that is, 15.8 percent and 11.2 percent. It appears from these reports that there is distinct lack of uniformity in the interpretation of the gross tissue changes produced by syphilis.

The same variability in diagnostic criteria is apparent in the reports based on microscopic evidence of syphilis. These include the reports of Guldberg (23) (5.8 percent), Koppisch (11.3 percent), Hala (21.1 percent), and Warthin (29.5 percent). The first of these authors found no greater incidence of syphilis through the study of routine histologic preparations than did Teodori, Frates, or Symmers, all of whom relied predominantly on gross examination alone. The disparity between Guldberg's observations, on the one hand, and Warthin's, on the other, is so striking as to suggest that it results not so much from a real difference in the incidence of syphilis in the two populations as from significant differences in the diagnostic criteria followed by the two investigators.

The conclusion is warranted that there is a clear need for a restatement of the morphologic changes, both gross and microscopic, which result from syphilitic infection. This is especially true with regard to the histologic

alterations described by Warthin as definitive, and this aspect of the problem will be discussed in a subsequent chapter. Precise evaluation of the anatomic changes of syphilis in terms of morbidity and mortality will depend primarily on the standardization of diagnostic criteria and on the general adoption of a uniform nomenclature.

CHAPTER 3

MATERIAL AND METHODS OF ANALYSIS OF YALE AUTOPSY PROTOCOLS[1]

The previous chapter was devoted to a review of the literature on the frequency of the changes attributed to acquired syphilis in autopsies on individuals over 20 years of age. It was found that syphilitic changes observed at autopsy by 17 different reporters varied from a low incidence of 2.6 percent to a high of 29.5 percent with a combined average of 5.45 percent among 146,761 autopsied adults. A critical analysis of the wide discrepancies between the observations of different investigators was made, and it was concluded that the differences resulted largely because of the great variability in the criteria employed in arriving at a gross or microscopic diagnosis of syphilis.

Subsequent sections will be based primarily upon a study of the autopsies performed at the Yale University School of Medicine, together with supplemental information from the literature. This chapter will describe this material and discuss the methods employed in analyzing it. The punch-card code finally adopted for the survey is presented in the appendix. In addition, two samples from the nonsyphilitic population will be compared with each other and with the residue of the nonsyphilitic population with respect to age, sex, and race. It will be shown that these two groups represent a random selection from the total nonsyphilitic population in our autopsy series, and therefore can be used as standard nonsyphilitic controls for comparison with the syphilitic group.

Source of Autopsy Population

The material available for examination and analysis consists of the hospital records, autopsy protocols, and microscopic sections of 5,300 consecutive autopsies performed at the Yale University School of Medicine in the period from September 22, 1917, to March 8, 1941. These necropsies were conducted by various prosectors affiliated with the Department of Pathology during this period. The largest proportion of subjects were referred for necropsy by the New Haven Hospital, which is a nonprofit association serving primarily the city and county of New Haven, but receiving patients also from other communities in the State and occasionally from outside the State. In 1917, 4,529 patients were admitted. During the course of the next 24 years, the capacity increased to 524 beds in 1941, and 12,670 patients were admitted during the fiscal year 1940-41. Of the 524 beds, 330 were reserved for ward patients, 88 for semiprivate patients, and 106 for private patients. From September 1917 to July 1940 a total of 9,162 admitted patients of both sexes and of all ages died. Of this number, 4,371, or 48 percent, were autopsied, and 69 percent of these autopsies were upon individuals aged 20 years or more.

The city of New Haven, in which most of the patients entering the New Haven Hospital reside, is a manufacturing and university community whose inhabitants are largely Caucasian, numbering approximately 162,000. The population has been fairly constant at this level during the last 20 years, foreign-born whites comprising approximately 20 percent. In the census of 1940 there were 6,235 Negroes—about 4 percent of the total population.

The 5,300 consecutive autopsies noted above included 3,907 necropsies on individuals of both sexes aged 20 years and over. Of these, 3,187 died at the New Haven Hospital and 96 at the affiliated William

[1]This chapter and the appendix are revisions of the article *Studies in Syphilis. II. Methods of Analysis of Yale Autopsy Protocols,* by Bernard Black-Schaffer and Paul D. Rosahn, which was published in the *Yale Journal of Biology and Medicine,* vol. 15, p. 575, 1943.

Wirt Winchester Tuberculosis Hospital. An additional 438 died at State tuberculosis sanitoriums, at other hospitals, or at home, and 186 were coroner's cases where death occurred before admission to the New Haven Hospital.

Selection of Syphilitic Group

The complexity of analyzing a large autopsy population by the old hand method of sorting and tabulating is at once apparent. The punch-card system of analysis lends itself conveniently to this type of survey and was therefore adopted. Rosahn (*24*), in 1938, described the application of the Hollerith punch-card system to the analysis of autopsy protocols, and the first 4,000 autopsies in this series represent the same cases coded by him in 1938. The additional 1,300 cases which brought the total to 5,300 were coded and punched according to the manner described by Rosahn in his original communication. These 5,300 cards were sorted according to age, and 1,393 autopsies on patients under 20 years of age were eliminated. As indicated previously, age 20 has been taken arbitrarily as the lower age limit of acquired syphilis. It is recognized that this procedure may result in the inclusion of a small number of syphilitic individuals whose infection is of congenital origin, but these are counterbalanced by excluding persons under 20, some of whom may have the lesions of acquired syphilis.

The remaining 3,907 cards representing individuals aged 20 or more were then sorted for syphilitics and for suspected syphilitics. The criteria employed in choosing these cases were as follows: (1) A past history of primary or secondary infection or a positive serologic reaction; (2) a history of antisyphilitic therapy; (3) a positive serologic reaction during the last admission or significant findings in the spinal fluid; (4) a clinical diagnosis of syphilis; (5) a positive serologic reaction at post-mortem; (6) an anatomic diagnosis consistent with syphilis. The clinical charts for all cases meeting any one of the above criteria were obtained wherever possible, and critically evaluated. In addition, the clinical records of all patients with a known family history of syphilis were also studied. A total of 380 cases diagnosed as syphilitic on clinical or laboratory or postmortem evidence remained, and this group hereinafter will be referred to as the "experimental" or "syphilitic" group. It should be noted at this point that 380 out of 3,907 adults in our series, or 9.7 percent, presented a clinical history consistent with a diagnosis of syphilis, or findings at autopsy consistent with such a diagnosis, or both. This represents the aggregate incidence of syphilis in our adult autopsy population and will receive further comment.

Selection of Control Group

In order to facilitate comparisons between the experimental group and nonsyphilitics, 2 control groups of nonsyphilitics were established, each of which contained the same number of individuals as the experimental group. The purpose of selecting 2 control groups was to test each against the other as regards race, sex, and age distribution in order to verify the method devised for random sampling. This method consisted in arranging each of the 380 cards comprising the experimental group in sequential order by autopsy number and similarly arranging each of the remaining 3,527 cards representing the total nonsyphilitic population. The first group of controls hereinafter designated as "control group A" was selected by taking the first card in the nonsyphilitic series following each card for a syphilitic, and the second control group, hereinafter designated "control group B," was similarly derived by segregating from the nonsyphilitic population the fifth card following that for each syphilitic. In this way 2 control groups were established having the same temporal distribution in our autopsy series as the syphilitic group.

Comparison of Control Groups with Total Nonsyphilitic Population

To establish the reliability of control groups A and B as random samples from the total nonsyphilitic population, they were classified as to sex, race (white and nonwhite), and age.

Sex

There were 226 males (59.5 $\pm$ 2.52 percent) among the 380 individuals in control

group A; 238 males (62.6 ± 2.48 percent) among the 380 in control group B; and 2,232 males (63.3 ± 0.81 percent) among the 3,527 individuals comprising the entire nonsyphilitic population. No significant differences exist among these values and it can be concluded that as regards sex the 2 control groups represent a random selection from the nonsyphilitic autopsy population.

Race

Control group A had 363 white individuals or 95.53 ± 1.06 percent of the total in the group; control group B had 358 white persons or 94.21 ± 1.20 percent of the total; and the total nonsyphilitic population of 3,527 had 3,314 whites or 93.96 ± 0.39 percent. The remaining individuals were Negroes, with one exception, an Oriental. The differences among these values are statistically nonsignificant, so that the 3 groups are homogeneous as regards color.

Age

The decennial age distribution of white and nonwhite males and females comprising control groups A and B and the residue of the nonsyphilitic population is shown in tables 6 and 7. No significant differences were encountered by applying the chi-square test of homogeneity. (White males: Chi-square = 11.66, N = 12, P = 0.476, not significant. White females: Chi-square = 13.09, N = 12, P = 0.369, not significant. Nonwhite males: Chi-square = 0.56, N = 4, P = 0.966, not significant. Nonwhite females: Chi-square = 2.71, N = 4, P = 0.611, not significant.) So far as age is concerned the control groups represent a random selection from the total nonsyphilitic population.

The above analysis indicates that with regard to sex, race, and age the two control groups can be used as representative of the total nonsyphilitic population in making comparisons with the experimental group. This method of comparison will be used wherever necessary in subsequent chapters.

Code for the Study of Syphilis

Following the selection of the syphilitic and control groups, a new code was drawn up with the object of extracting as much pertinent information as possible concerning syphilis and related states. Wherever they were available, the clinical records of these three groups were obtained and the required information derived from them. Moreover, the autopsy protocols were re-examined and the tissues were subjected to further microscopic study. The code as finally utilized appears in the appendix, and using this code, new cards were punched for the syphilis group and for the two control groups. In coding diagnoses the *Standard Nomenclature of Disease* classification was employed, with minor modifications to conform to the study.

TABLE 7.—*Age and sex distribution of nonsyphilitic nonwhite individuals in Yale autopsy series*

Group	Sex	20–39 years	40–59 years	60+ years	Total	Age unknown
Control A	Male	3	5	2	10	0
	Female	1	5	1	7	0
Control B	Male	4	4	2	10	0
	Female	4	4	3	11	1
Residue	Male	37	40	24	101	12
	Female	25	26	19	70	1
Total	Male	44	49	28	121	2
	Female	30	35	23	88	2
Total		74	84	51	209	4

¶ 1 Oriental.

TABLE 6.—*Age and sex distribution of nonsyphilitic white individuals in Yale autopsy series*

Group	Sex	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years	80+ years	Total	Age unknown
Control A	Male	24	29	36	47	33	31	11	211	5
	Female	7	26	24	31	28	20	8	144	3
Control B	Male	23	28	38	58	47	23	7	224	4
	Female	17	16	18	28	22	18	10	129	1
Residue	Male	156	170	346	359	342	193	68	1,634	31
	Female	128	142	148	185	180	104	39	926	2
Total	Male	203	227	420	464	422	247	86	2,069	40
	Female	152	184	190	244	230	142	57	1,199	6
Total		355	411	610	708	652	389	143	3,268	46

FIBROSIS AND ROUND CELL INFILTRATION OF THE PARENCHYMATOUS ORGANS (WARTHIN) IN THE TISSUE DIAGNOSIS OF SYPHILIS [1]

In chapter 2 evidence from autopsy studies by different investigators has been cited which indicates the wide variability in the incidence of tissue changes attributed to syphilitic infection. The frequency of morphologic evidence of syphilis among individuals aged 20 and over ranges, according to different reporters, between the extremes of 2.6 and 29.5 percent. Analysis of our own material gave an incidence of 4.0 percent. Certain variables which might have contributed to the widely different incidence rates were critically reviewed, and it was concluded that the lack of uniform criteria for the tissue diagnosis of syphilis was the most important factor involved. The highest rates were reported by investigators who followed the criteria defined by Warthin (5), while those reporting the lowest incidence either antedated Warthin or did not adopt his teachings.

The Warthin Lesion

Warthin's original description (5) of the lesion which he interpreted as indicating syphilitic infection follows:

Heart.—The heart in every case showed microscopic lesions characteristic of spirochete localization . . . The cardiac lesions in the cases in which syphilitic infection was known to exist, and in those in which it was not suspected are identical. They vary greatly in degree . . . It must be emphasized that the determination of cardiac syphilis is essentially microscopic . . .

The essential lesion of cardiac syphilis is an interstitial myocarditis characterized by infiltrations of lymphocytes and plasma cells along the vessels between the muscle fibers. These infiltrations are usually patchy or diffuse, very rarely focal or circumscribed . . . The infiltrations vary in degree, but usually are slight, the cells often being arranged in close single file between the fibers . . . The cells of the infiltrations are probably chiefly histogenetic lymphocytes and young formative cells. Large epithelioid fibroblasts are very common, especially in the older, healing areas . . .

. . . In the most severe cases larger areas of infiltrations are grouped around the coronary arterioles. These may reach such a size as to suggest miliary gummata . . .

. . . In the older healed areas the stroma becomes fibroid and hyaline. In the great majority of cases the myocardium shows healed, fibroid areas in association with the active infiltrations. In many cases the fibroid areas predominate and search may be necessary to show the presence of active infiltrations. This is true especially of the older unrecognized cases. In every case, however, such active areas have been found, and no completely healed cases have been seen. A progressive fibrosis of the myocardium always takes place. In acquired syphilis the fibroid areas are always larger on the endocardial side; but in some cases they have extended completely through the myocardium . . . These marked changes practically always occur just above the apex, in the anterior wall of the left ventricle; . . . The 'fibroid' heart is the ultimate outcome of all cases of latent syphilis.

Pancreas.—The pancreas in all of the old cases of syphilis showed a greater or less degree of atrophy and interstitial fibrosis. In the majority of cases the changes were irregularly scattered throughout the organ, the body and the tail portions showing an especial tendency to involvement. Lobules showing marked change may be surrounded by those showing no change. In other cases the entire pancreas showed a diffuse fibrosis, varying from slight to the most marked degree. The connective tissue increase is both inter- and intralobular. In the majority of cases it was old, containing few cells . . . Careful search has revealed, however, in every case active

[1] This chapter revises the article *Studies in Syphilis. V. An Evaluation of Fibrosis and Round Cell Infiltration of the Parenchymatous Organs (Warthin) in the Tissue Diagnosis of Syphilis,* by Paul D. Rosahn and Bernard Black-Schaffer, which was published in the *American Journal of Syphilis, Gonorrhea & Venereal Diseases,* vol. 28, p. 142, 1944.

areas of plasma-cell infiltration. These areas often show an edematous or myxomatous connective tissue, the plasma-cells and lymphocytes may be few or many . . .

As to the syphilitic nature of these lesions, they are identical with those produced by the spirochete in other tissues and organs. The localized plasma-cell infiltrations, slight fibroblastic proliferation, edematous or mucoid stroma eventually fibrosis, are histologically specific characteristics, I believe . . .

Adrenals.—Small infiltrations of plasma-cells and lymphocytes are of constant occurrence in the adrenals of cases having known syphilis and unsuspected latent syphilis. In the great majority of cases these infiltrations are slight. They occur usually in the medullary portion or in the inner portion of the reticular zone of the cortex. They are usually perivascular. Fibroblastic proliferation of the stroma or fibrosis may or may not be present; the capsule of the organ is usually thickened, and perivascular infiltrations of small size occur in the surrounding tissues. The walls of the blood vessels usually are thickened . . .

Liver.—The liver showed chronic passive congestion and atrophy (brown atrophy chiefly) in every case. Gummata were found in 5 cases, hepar lobatum in 8, atrophic cirrhosis in 10 and an intralobular cirrhosis in 1, Glissonian cirrhosis in 3 cases, while localized fibrosis was very common. The inflammatory lesions varied from slight plasma-cell infiltrations of the periportal tissue to the most marked cirrhotic changes. The relationship of these latter changes to syphilis has not been absolutely determined except in a few cases in which spirochetes were found in such infiltrations . . .

Testis.—In all of the male cases the testes showed varying degrees of atrophy and fibrosis. In the more active cases plasma-cell and lymphocyte infiltration between the tubules, fibroblastic proliferation of the stroma, thickening of the basement membrane and diminished spermatogenesis are the chief changes. These changes may involve the entire organ, or occur in small scattered patches. In the older cases the germinal epithelium of the tubules may be entirely lost, the tubules collapsed, and represented entirely by the hyaline-thickened basement membrane . . . The interstitial cells remain preserved, and in many cases appear hypertrophic. The stroma between the tubules is thickened and hyaline. In severe cases the entire testis becomes fibroid . . .

It is common knowledge that most American pathologists have not accepted Warthin's concept of the tissue changes described in detail above. Nevertheless, a few pathologists have adopted his criteria, and this has led many clinicians to conclude that questionable syphilitic lesions such as chronic syphilitic myocarditis, syphilitic gastric ulcer, and diffuse syphilitic hepatitis are well-established pathologic entities. In the many years that have elapsed since Warthin's original paper, no organized systematic investigation has been made to verify the point of view he espoused. In the present chapter an attempt will be made to evaluate Warthin's dicta for the diagnosis of syphilis of the parenchymatous organs, through the use of recognized statistical technics.

Material and Methods

The analysis is based on a comparison of the incidence of fibrosis and round cell infiltration (hereafter termed the "Warthin lesion" in the interest of brevity) in the parenchymatous organs of 2 populations. The first group, described in chapter 3, consists of 380 syphilitics, so diagnosed by historical, clinical, laboratory, or post-mortem evidence. They were selected from among 3,907 autopsies on persons aged 20 years or over, performed at the Yale University Department of Pathology from 1917 to 1941. The second group is the residue of 3,527 nonsyphilitic persons in the series. Each member of this population was regarded as nonsyphilitic because none presented historical, clinical, laboratory, necropsy, or other acceptable evidence of syphilitic infection. In order to deal conveniently with this large population of nonsyphilitics, 2 random samples of 380 persons each were drawn from it and labeled "control group A" and "control group B." The method devised for this random selection, and evidence that as regards age, sex, and color, control groups A and B are actually random samples from the larger nonsyphilitic population, have been presented in chapter 3. Since homogeneity between these groups has been demonstrated, thus verifying the random sampling method, they have been combined and are treated as one group in the ensuing analysis. A later chapter will demonstrate that the mean age at death of both the syphilitic and the nonsyphilitic Negro groups in our series was significantly lower than the comparable mean values for whites. Because of this observation, the data on Negro persons have been excluded from the analysis.

Breakdowns into sex groups have not been attempted in order not to reduce the size of the statistical samples. The group finally available for analysis consisted of 283 syphilitic and 722 nonsyphilitic white persons.

The frequency of the Warthin lesion in the syphilitic group was compared with its frequency in the control group. All such comparisons were conducted by the method of chi-square. In the statistical procedures significance has been attached to values of $P \leq 0.01$; that is, when the probability of an event occurring by chance was 1 or less than 1 in 100, the result was considered significant.

The review of the histologic preparations was conducted in sequence according to autopsy number and without knowledge as to whether the case under examination belonged to the syphilitic or nonsyphilitic group. This procedure effectively eliminated any unconscious bias that might have been present in the reviewer's mind. Because of Warthin's emphasis on the diagnostic value of the changes in the heart, pancreas, adrenal, liver, and testis, these organs were singled out for examination. The histologic changes sought and their quantitative groupings are given in the appendix under columns 45 to 49 inclusive.

During these microscopic studies repeated reference to Warthin's *New Pathology of Syphilis* was made in order to maintain as constant a standard of diagnosis as possible. Figures 1 to 15 are representative of the tissue changes encountered.

The preparations were fixed in Zenker's solution, rarely in formalin, and embedded in paraffin. The great majority were stained with hematoxylin and eosin, although scattered slides were stained by the methods of van Gieson, Mallory, Heidenhain, and Masson. A small number of Levaditi preparations were present, but no attempt was made to verify the presence or absence of treponemes. The number of slides available was not uniform in each case. In some, only one slide from each organ was on file, in others the sets were incomplete, and in still others, multiple sections of various organs were available, dependent to a large degree on the interest and thoroughness of the individual prosector.

Comparison of Warthin Lesions in the Parenchymatous Organs of Syphilitic and Nonsyphilitic White Persons

General Comments

Early in the survey it became apparent that there was an absence of any qualitative difference between the fibrosis and round cell infiltration observed in the organs of syphilitic persons, and that found in the organs of the nonsyphilitic controls. The distribution of these lesions and their morphologic characteristics were essentially the same in the two groups, which were indistinguishable one from the other on the basis of Warthin's criteria. Moreover, the amount of fibrous replacement and the intensity of the lymphocytic and plasma cell infiltration were extremely variable in both populations, so that the quantitative aspects of these changes could not be utilized in differentiating the syphilitic from the nonsyphilitic groups.

Heart.—When lesions were noted, fibrosis of the interstitium predominated, with varying numbers of plasma cells and lymphocytes. In many instances fibrosis was the outstanding feature but in all such cases, a few scattered round cells could be located on careful search. No effort was made to segregate lesions with predominant fibrosis from those with a cellular infiltration as the outstanding feature. It was observed, however, that the fibroid zones were more prominent beneath the endocardium than in relation to the epicardium. This distribution appeared to occur with equal frequency among the nonsyphilitics and the syphilitics, but the quantitative aspects of this occurrence were not investigated statistically.

Pancreas.—Here also the outstanding change was in the extent of the fibrous tissue deposits, rather than in the numbers of infiltrating inflammatory cells. In rare instances lymphocytes and plasma cells were present in the absence of connective tissue replacement. Occasionally careful search was necessary in order to locate inflammatory cells in cases where fibrosis predominated.

Adrenals.—Small round cell infiltrations were noted in many instances. These occurred most frequently in the medulla.

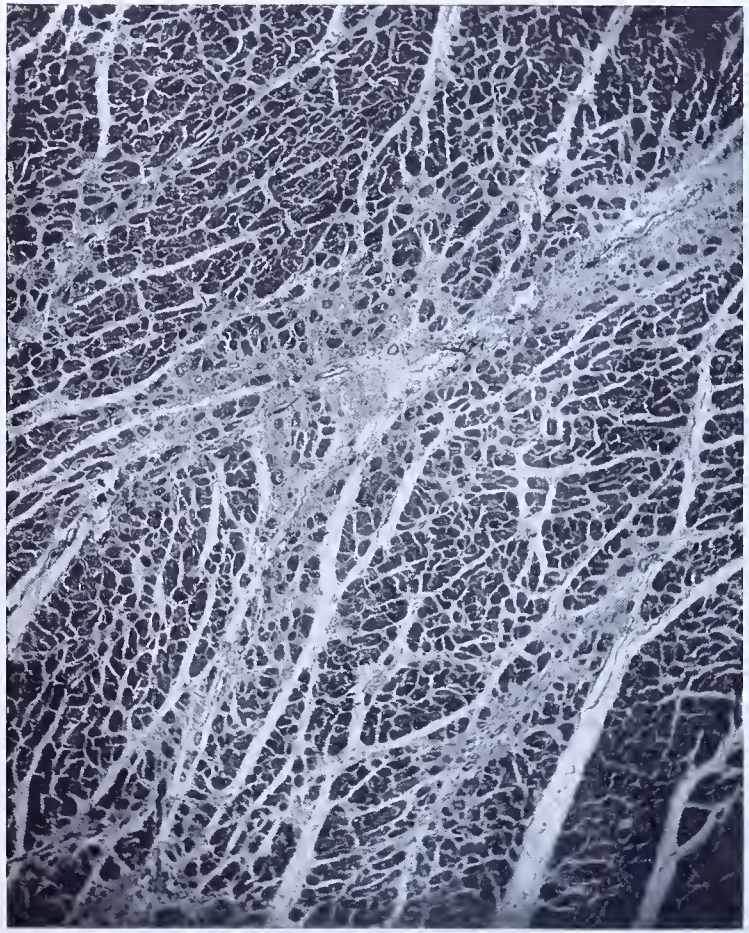

FIGURE 1.—Heart showing minimum fibrosis and round cells. Control case. (× 40)

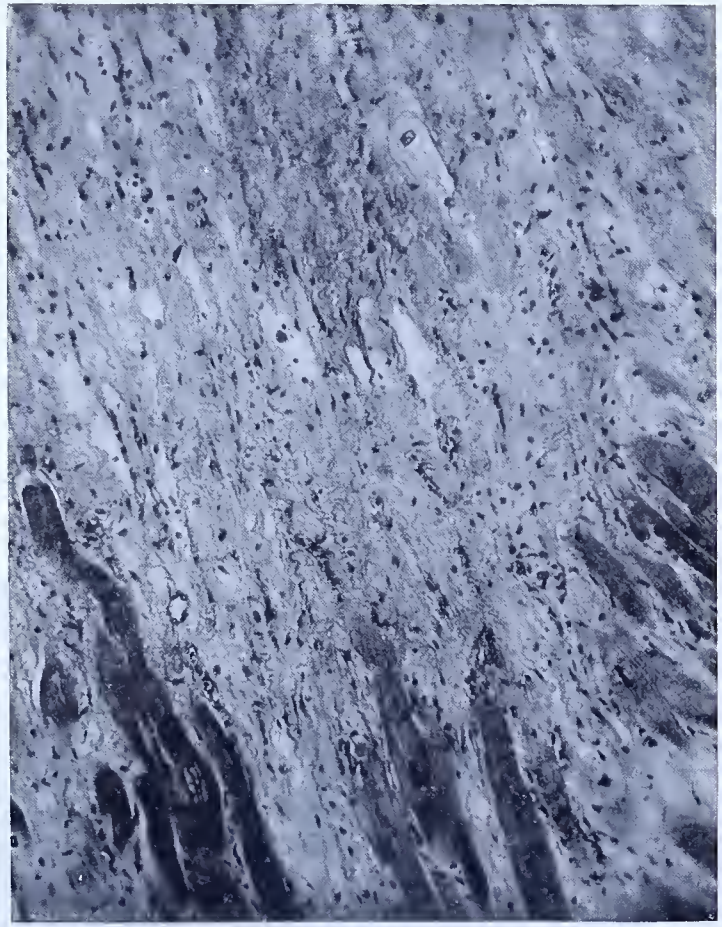

FIGURE 2.—Heart showing maximum fibrosis and round cells. Control case. (× 175)

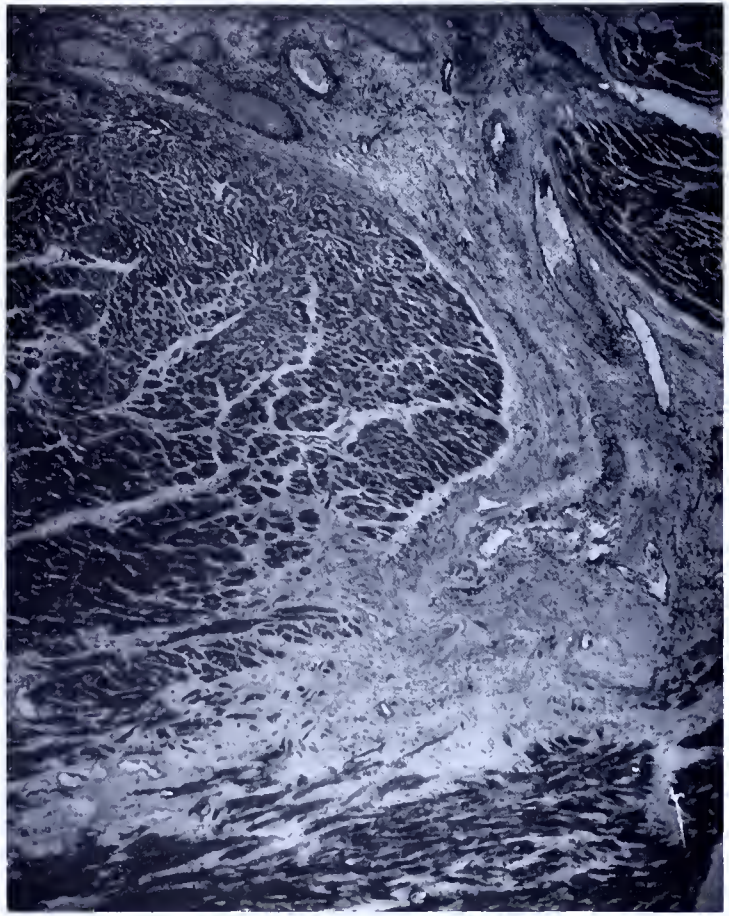

FIGURE 3.—Heart showing intermediate fibrosis and round cells. Control case. (× 40)

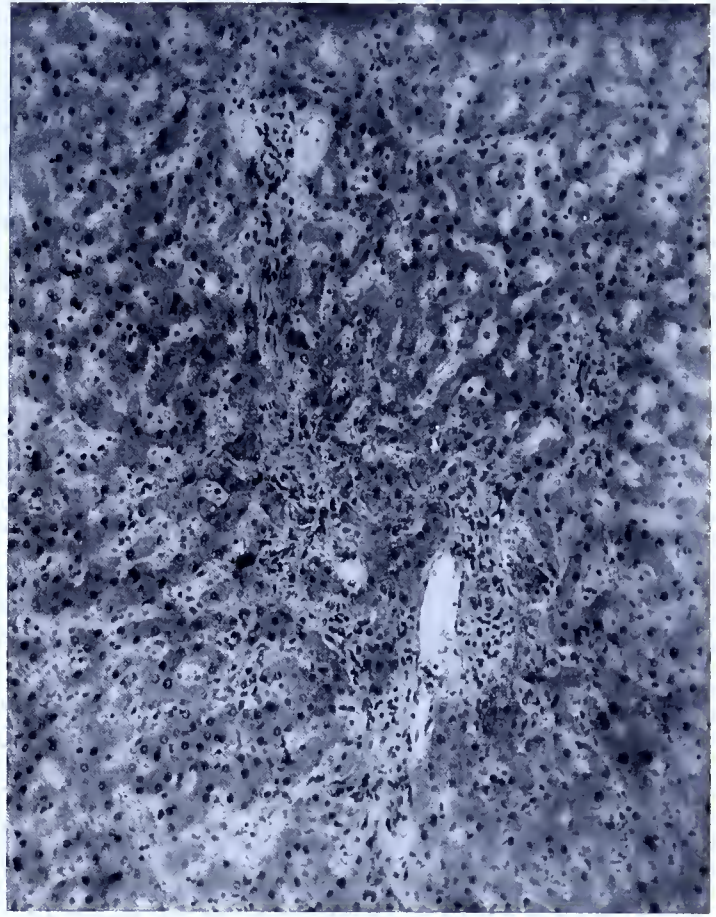

FIGURE 4.—Liver showing minimum fibrosis and round cells. Syphilitic case. (× 175)

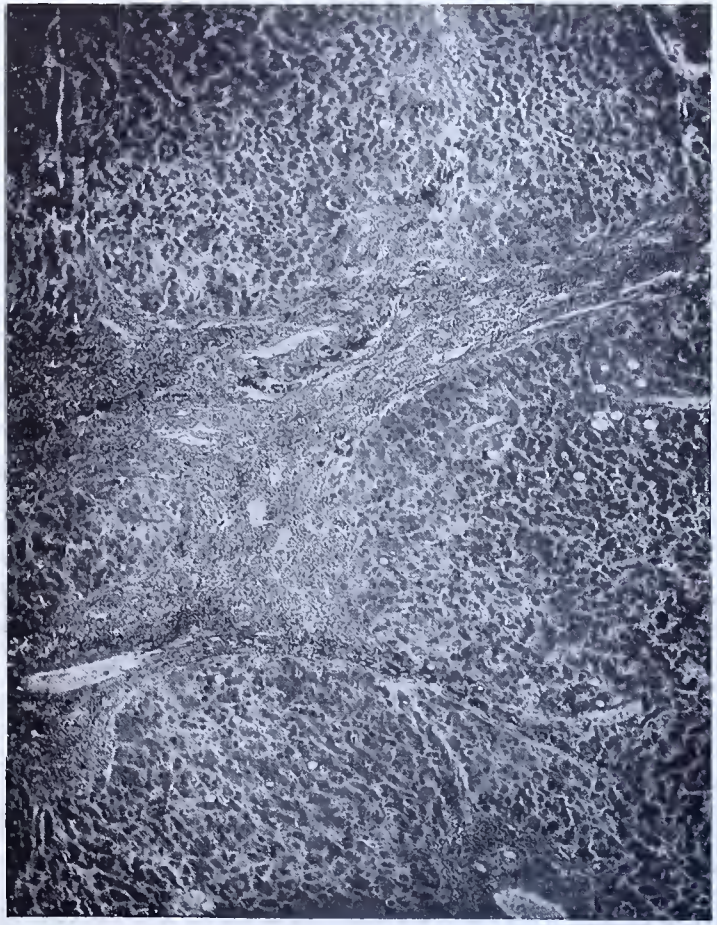

FIGURE 5.—Liver showing maximum fibrosis and round cells. Control case. (× 50)

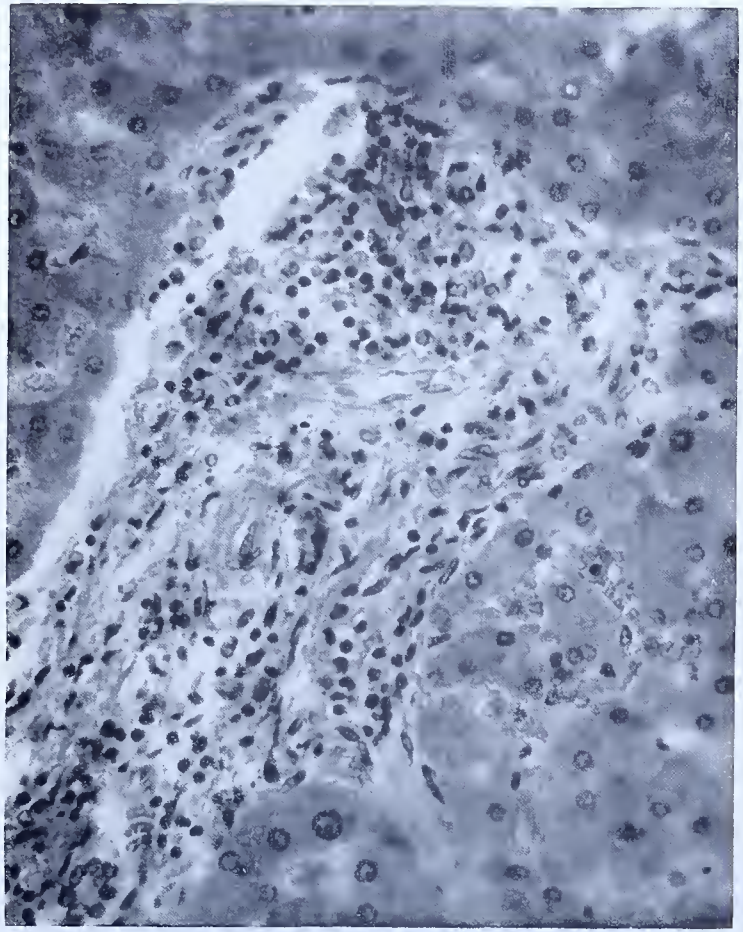

FIGURE 6.—Liver showing round cells. Control case. (× 150)

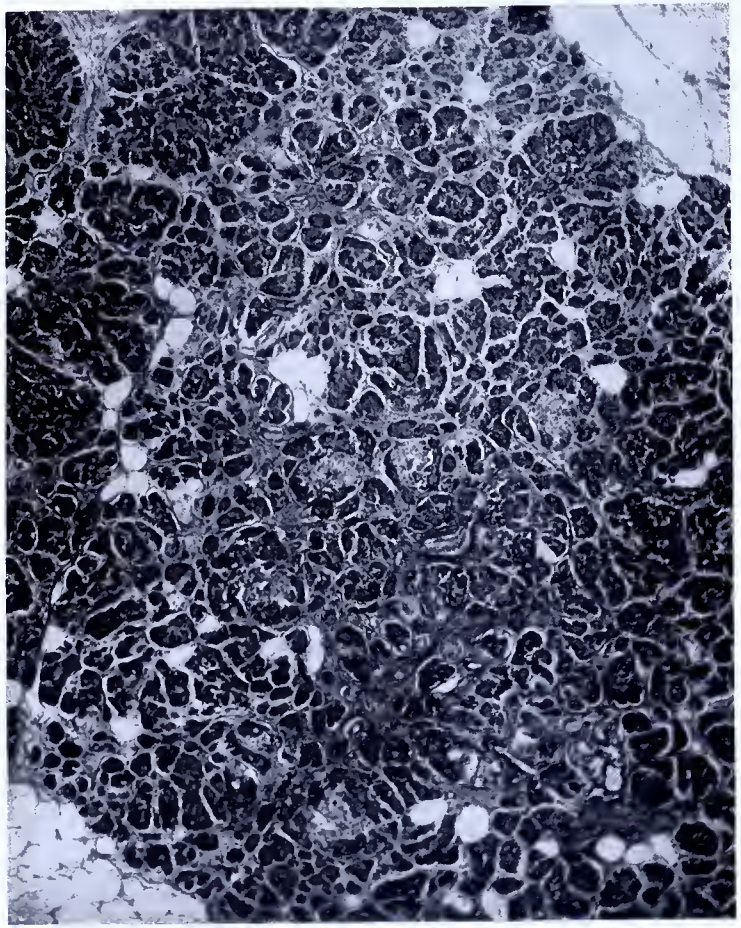

FIGURE 7.—Pancreas showing minimum fibrosis and round cells. Control case. (× 50)

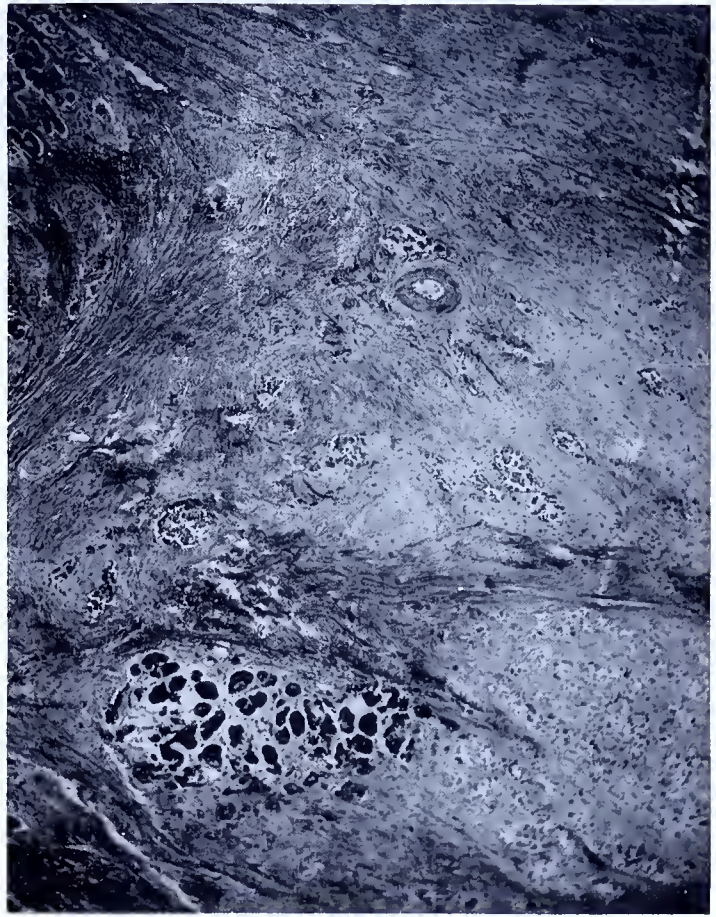

FIGURE 8.—Pancreas showing maximum fibrosis and round cells. Syphilitic case. (× 50)

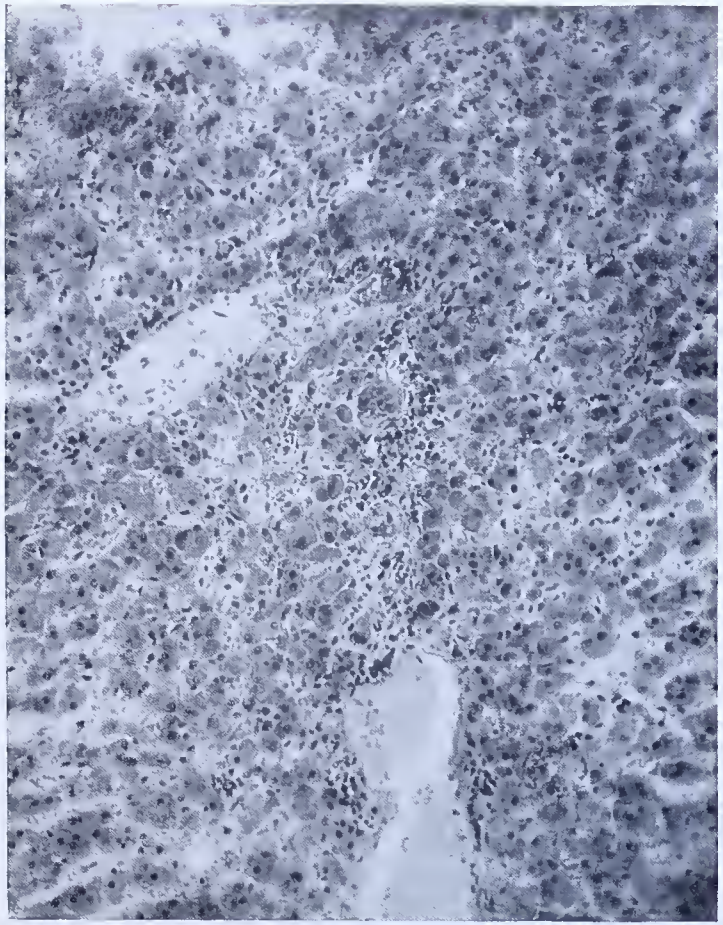

FIGURE 9.—Adrenal showing minimum fibrosis and round cells. Control case. (× 175)

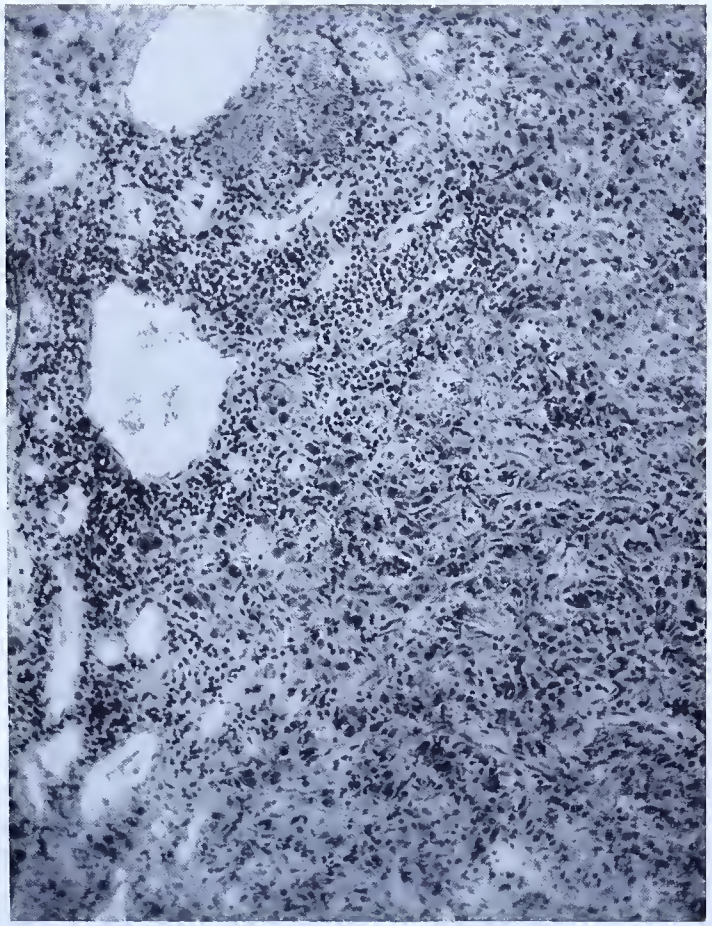

FIGURE 10.—Adrenal showing maximum fibrosis and round cells. Syphilitic case. (× 175)

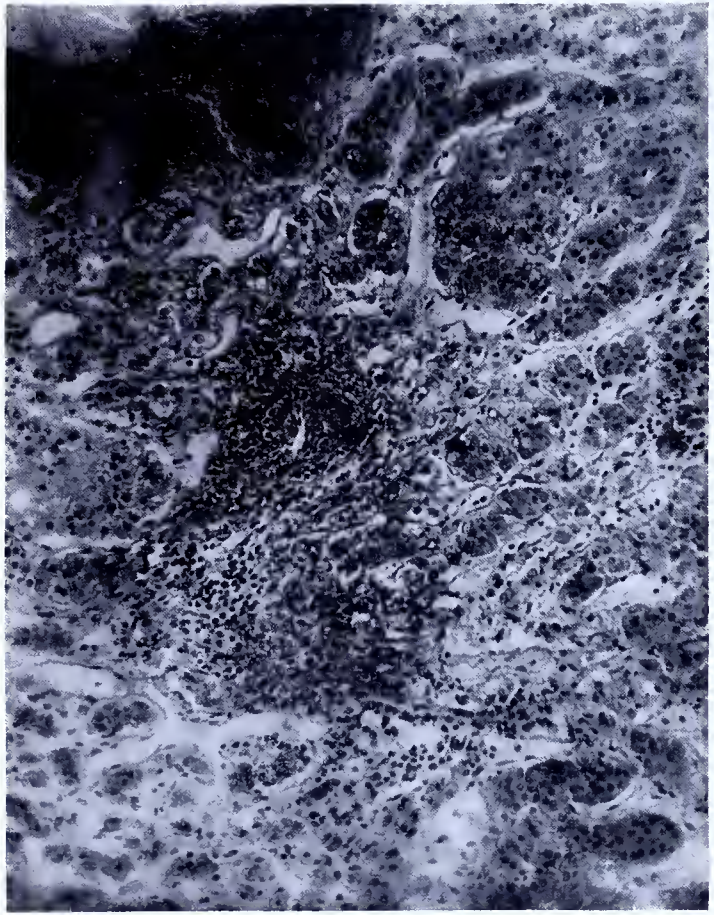

FIGURE 11.—Adrenal showing intermediate round cells. Control case. (× 175)

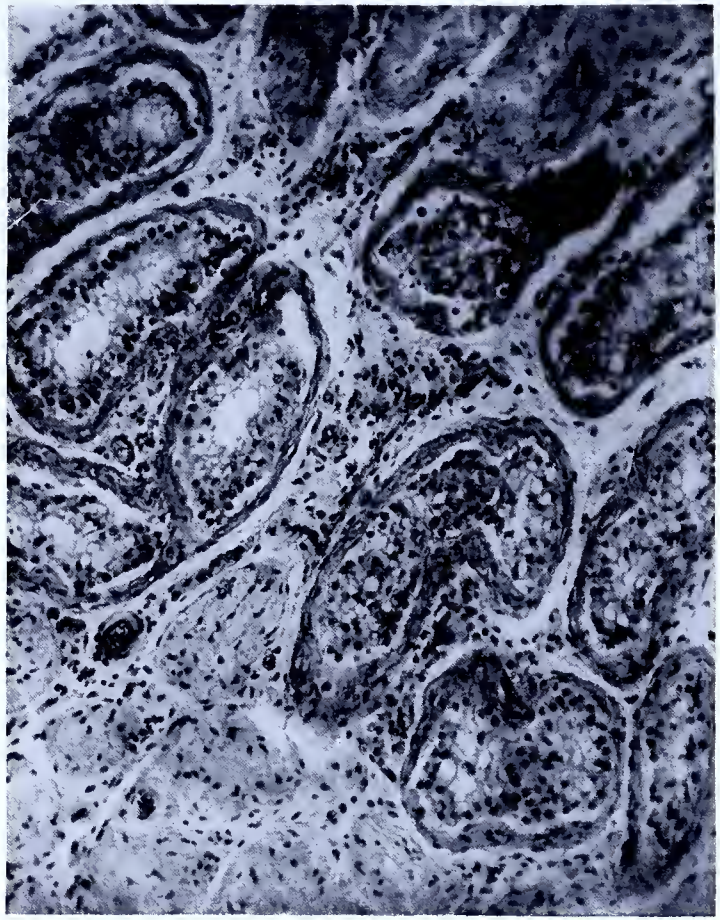

FIGURE 12.—Testis showing minimum fibrosis and round cells. Control case. (× 175)

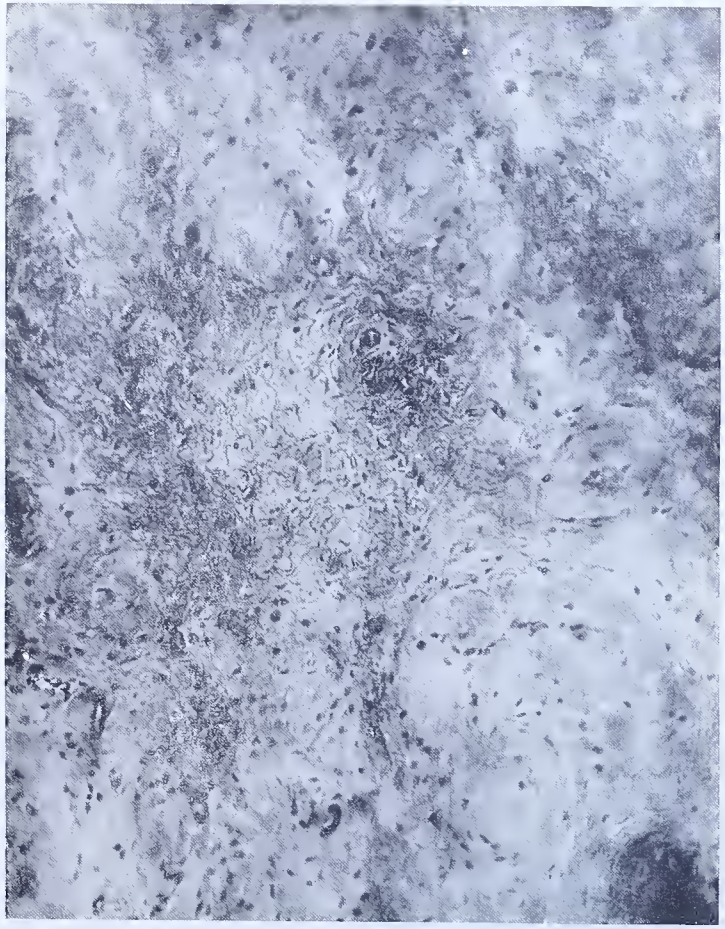

FIGURE 13.—Testis showing maximum fibrosis and round cells. Control case. (× 175)

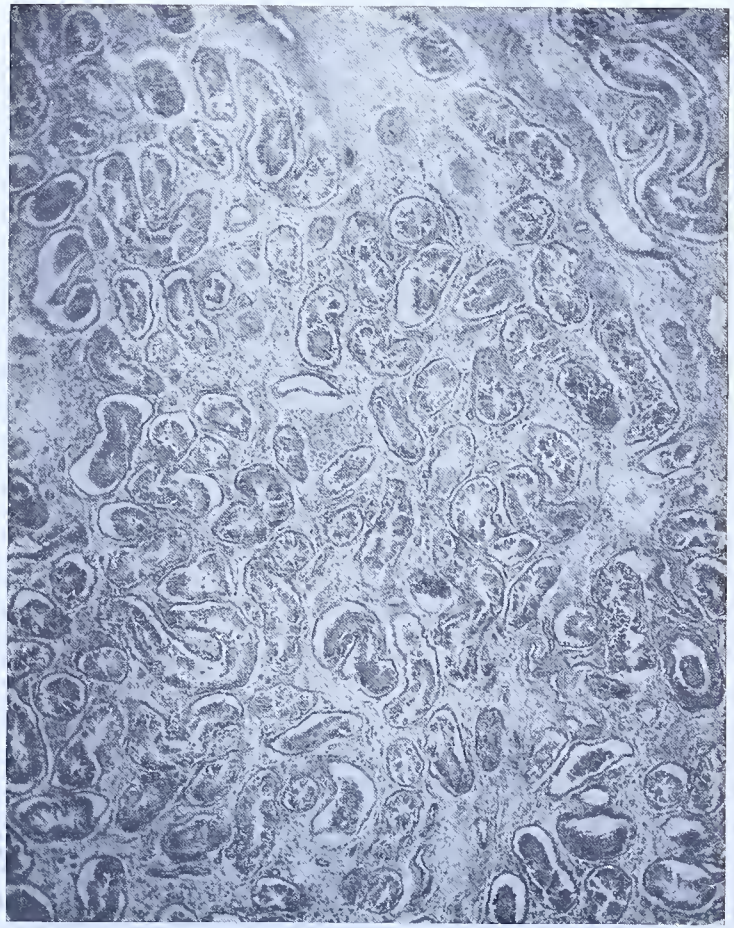

FIGURE 14.—Testis showing maximum atrophy. Syphilitic case. (× 40)

FIGURE 15.—Testis showing maximum fibrosis. Control case. (× 40)

Fibrous tissue deposition was observed so rarely that it did not appear feasible to set up a separate classification based on its presence.

Liver.—Portal fibrosis with lymphocytic and plasma cell infiltration was extremely variable in degree. A group of cases was segregated because of infiltrating inflammatory cells in the portal spaces, in the absence of any increased deposits of connective tissue. These cases were coded under column 46, No. 4, and do not appear in the computations of table 8.

Testis.—Atrophy of the tubules with varying degrees of interstitial fibrosis and cellular infiltrates was the outstanding finding. In many instances the tubular atrophy with basement membrane thickening dominated the picture, but scanty deposits of fibrous tissue and minimal numbers of mononuclear cells were also present.

Incidence

Because of the failure to demonstrate any qualitative differences between Warthin lesions in the organs of syphilitic persons in comparison with nonsyphilitics, other methods of comparison were indicated. These were essentially of a statistical nature. It was concluded that the crucial test of the Warthin hypothesis rested on the demonstration that the lesion which he considered pathognomonic of syphilitic infection occurred more frequently in a population of syphilitic persons than in a population of nonsyphilitics. If such were the case, and if the difference could be shown by statistical methods to be outside the realm of chance occurrence, considerable weight would be added to Warthin's conclusions. Final proof would still be lacking, however, since even if the Warthin lesion were more frequent in a syphilitic than in a nonsyphilitic population, such a finding might be the result of an as yet unknown independent variable other than specific infection. On the other hand, if the two populations did not differ from each other, or if the Warthin lesion were found in a greater proportion of persons without syphilis than in those known to be infected, the conclusion that the Warthin lesion is nonspecific and due to factors other than syphilitic infection would seem to be justified. These considerations have been kept in mind in the construction of table 8, in which is shown the frequency of Warthin lesions of the heart, pancreas, adrenals, liver, and testes in the syphilitic and nonsyphilitic groups.

The proportion of syphilitic persons and of the nonsyphilitic control population with Warthin changes in the heart was essentially the same, and the two groups were also no different as regards Warthin changes in the adrenals, liver, and testes. For all of these organs chi-square was less than 3.841, the lower limit of significance, indicating that any observed difference between the two populations was well within the limits of sampling error.

Warthin lesions were observed in the pancreas of 39.8 percent of the syphilitic group and in 30.8 percent of the controls. These two values are probably significantly different (chi-square = 5.61, P = 0.02—), that is, the observed difference would be expected to occur by chance alone about twice in a hundred such comparisons. The pancreas was

TABLE 8.—*Frequency of Warthin lesions in the parenchymatous organs of syphilitic and nonsyphilitic persons*

Organ	Code for Warthin lesions		Group	Number examined	Lesions found		Chi-square
	Column	Number			Number	Percent	
Heart	49	2, 3, 4	Syphilitic	239	90	37.7	0.01
			Control	612	233	38.1	
Pancreas	47	2, 3, 4	Syphilitic	211	84	39.8	5.61
			Control	568	175	30.8	
Adrenal	48	2, 3, 4	Syphilitic	186	60	32.3	2.75
			Control	502	130	25.9	
Liver	46	1, 2, 3	Syphilitic	237	70	29.5	0.03
			Control	603	182	30.2	
Testis	45	2, 3, 4	Syphilitic	81	44	54.3	2.38
			Control	151	66	43.7	

NOTE: n=1: Chi-square=6 635, P=0 01; Chi-square=3 841, P=0 05.

thus the only organ of the five studied in which Warthin lesions appeared to occur more frequently among syphilitic persons than among those without specific infection, but the difference here was only probably significant.

In the study of the liver sections a group was segregated because of the presence of round cells in the portal fields without any apparent accompanying fibrosis. This particular tissue change was coded as No. 4, column 46, and does not appear in table 8. It was thought that the frequency of this lesion in the syphilitic and nonsyphilitic populations might throw some light on its etiology and it was therefore investigated. The change was noted in the livers of 109 of the 237 syphilitic persons, and in 295 of the 603 persons comprising the nonsyphilitic group (table 9). The proportion of individuals with this liver lesion in the 2 groups was essentially the same (chi-square = 0.59, N = 1, P = 0.4+) so that specific infection can be excluded as the causative factor.

TABLE 9.—*Frequency of portal round cells without accompanying fibrosis in the livers of syphilitic and nonsyphilitic persons*

	Syphilis present		Syphilis absent		Total
	Observed	Estimated	Observed	Estimated	
Warthin lesions present..	109	114	295	290	404
Warthin lesions absent ..	128	123	308	313	436
Total.....	237	237	603	603	840

NOTE: n=1, Chi-square=0.59

Of the five organs investigated, the pancreas was the only one in which Warthin lesions occurred significantly more frequently among syphilitics than among nonsyphilitics, and even here the difference was not clearly outside the realm of chance. As indicated in an earlier paragraph, even if this difference were accepted as highly significant, the explanation of the relatively large proportion of nonsyphilitics with the identical lesion is not readily at hand. If syphilitic infection is accepted as one of the agents involved, other factors are certainly operative also. Extending this process of reasoning, the Warthin lesion cannot be accepted as pathognomonic of syphilitic infection by the very fact of its high incidence among uninfected persons. The argument may be presented that the Warthin change is pathognomonic, and by virtue of its presence, the so-called nonsyphilitic persons in our series are actually syphilitic. To this suggestion only one response can be made, that is, the care with which our group of nonsyphilitic persons was selected. None of them had any historical, clinical, or laboratory evidence of the disease, and none of them presented any of the classical changes at autopsy customarily associated with syphilitic infection.

Comparison of Frequency of Warthin Lesions Among Syphilitics With and Without Anatomic Lesions at Autopsy

Comparisons similar to those of the preceding section were made between two groups of syphilitics, one with classical anatomic lesions of syphilis at autopsy, and the other with none of the morphologic changes which in these reports have been accepted as indubitably syphilitic in origin. The criteria for the anatomic diagnosis of syphilis which have been followed in these reports include definite anatomic changes of syphilis of the central nervous system, vascular tree, bone, and parenchymatous organs including liver. Presumptive evidence of syphilis such as orchitis fibrosa, lingua glabia, and so-called syphilitic cirrhosis of the liver was not accepted as indicating morphologic syphilis. Warthin's criteria of lymphocytic and plasma cell infiltration with fibrosis in the parenchymatous organs were likewise not accepted as indicating anatomic evidence of syphilitic infection. The comparisons were conducted by means of the chi-square test of homogeneity, and are shown in table 10. In four of the five organs, any observed difference between the proportions of persons with Warthin lesions in the two groups can be explained by the error of random sampling. Only in the case of the adrenals is there an indication that the difference between the two groups is not due to chance, but even here the difference is not a highly significant one. Thus the presence or absence of definitive syphilitic

TABLE 10.—*Frequency of Warthin changes among syphilitic persons with and without anatomic lesions of syphilis at autopsy*

Organ	Anatomic lesions of syphilis present					Anatomic lesions of syphilis absent					Total	Chi-square
	Warthin lesions present		Warthin lesions absent		Total	Warthin lesions present		Warthin lesions absent		Total		
	Observed value	Expected value	Observed value	Expected value		Observed value	Expected value	Observed value	Expected value			
Heart	47	41.4	63	68.6	110	43	48.6	86	80.4	129	239	2.23
Pancreas	34	37.8	61	57.2	95	50	46.2	66	69.8	116	211	1.17
Adrenal	32	25.5	47	53.5	79	28	34.5	79	72.5	107	186	4.27
Liver	27	31.3	79	74.7	106	43	38.7	88	92.3	131	237	1.52
Testis	20	22.8	22	19.2	42	24	21.2	15	17.8	39	81	1.58

lesions was in general not a factor in the production of the tissue alterations described by Warthin.

The Frequency of Warthin Changes in Three Different Autopsy Populations

Between 1909 and 1929, Warthin studied 1,675 persons at autopsy. All were 25 years of age or over. Of this number 494 or 29.5 percent were diagnosed as syphilitic. His findings (*5*) giving the incidence of syphilitic changes by organ in each of the two decades, are shown in table 11. Weller's (*22*) material was obtained from the Haitian General Hospital, Port au Prince, Haiti. The purpose of the study was "to determine (*a*) if the lesions found in this Haitian population in which yaws is so common are like those which in the temperate zone are attributed to syphilis, and (*b*) whether lesions of another type, unknown in a region in which yaws does not exist, would be encountered." Weller's observations, recast to include only persons over 21 years of age, are also shown in table 11.

Precise statistical comparisons of the three surveys are not necessary to demonstrate that our own findings more closely approximate those of Warthin than do those reported by Weller. This is of especial significance in the interpretation of the specificity of the Warthin lesion. Weller states: "Because of special interest in this field, we have established, in this laboratory, fairly definite criteria for the diagnosis of syphilis of these organs. While these criteria have not received universal acceptance, many have found, as we have, that they are of practical value in determining the presence of visceral syphilis in a general autopsy population . . . Continued observation of the visceral pathology of syphilis, with constant checking against clinical and serologic data and occasional successes in staining spirochetes in regions in which their demonstration is notoriously difficult, has led us to make relatively few changes in the criteria which Warthin proposed." His study of

TABLE 11.—*Frequency of Warthin lesions in five organs as reported by three different investigators*

Organ	Warthin						Weller			Yale series	
	1910–1919			1920–1929						Syphilitic	Non-syphilitic
	Cases	Lesions	Percent	Cases	Lesions	Percent	Cases	Lesions	Percent	Percent[1]	Percent[1]
Heart	169	113	66.9	330	216	65.5	142	18	12.7	37.7	38.1
Pancreas	163	72	44.1	328	98	29.8	[2] 115	[2] 6	5.2	39.8	30.8
Adrenal	153	47	30.7	320	145	45.3	138	34	24.6	32.3	25.9
Liver	165	46	27.8	328	102	31.1	139	14	10.1	29.5	30.2
Testis	137	118	86.1	264	203	76.9	78	42	53.8	54.3	43.7

[1] See table 8.
[2] Age distribution not given.

NOTE: Warthin's report is based on patients over 25 years of age, Weller's on patients over 21 years of age, and the Yale series on patients aged 20 and over.

the unity or duality of the two diseases, yaws and syphilis, led Weller to conclude that "one of three conditions must exist; either yaws and syphilis are essentially the same disease; or the group of patients here considered has an extremely high incidence of syphilis and the evidences of this disease alone are apparent in the viscera; or yaws and syphilis, if different diseases, produce identical visceral lesions." Weller found no higher, and in fact a lower, incidence of Warthin changes in a Negro population, 70 percent of whom show positive Kahn reactions, than were observed in our population of Caucasians, both syphilitic and nonsyphilitic. Either the Warthin lesion actually occurs less frequently among Negroes of Haiti, where yaws is very common, than it does among whites with and without syphilis, or the lesion represents a nonspecific change. The first of these alternatives appears unlikely in view of Weller's comments on the identity of yaws and syphilis.

The Warthin Lesion and the Aging Process

If the Warthin lesion is not pathognomonic of syphilitic infection, what factor or factors are responsible for its presence? Many possible causative determinants can be postulated, among which are nonspecific concomitant or antecedent infections, disorders produced by hormone imbalance or nutritional and more particularly vitamin deficiencies, and changes associated with increasing age. Each of these possibilities, as well as others not readily apparent, offers a fruitful subject for investigation, but the last is the only one which can be elucidated by our own material. Is there any relation between longevity and the incidence of Warthin lesions? Is tissue fibrosis with cellular infiltrates related to diminished local nutrition resulting from the vascular sclerosis accompanying increasing age? The phrase "aging process" is employed herein with the full knowledge that what we are dealing with may not be the aging process per se, but the fact that with increasing age there is increasing opportunity for exposure to factors both exogenous and endogenous which produce structural tissue changes.

In tables 12 and 13 are shown the incidence of Warthin lesions in the syphilis and control groups according to organ and decennia. The summated incidence of these lesions in persons under and over 60 years of age is also given in these tables, and depicted graphically in chart 5. From the tables it is seen that the proportion of cases in which Warthin lesions were found increases steadily in most tissues and in both groups, with increasing age. In the syphilis group the proportion of cases with Warthin changes in the heart, adrenal, liver, and testis was significantly greater in the "60 and over" class than in the "under 60" class. (Chi-square: heart = 8.46, adrenal = 12.33, liver = 6.85, testis = 10.80). Warthin lesions of the pancreas were found in a greater proportion of syphilitics in the "60 and over" group than in the

TABLE 12.—*Number of syphilitic cases examined and number and percent in which Warthin lesions were found, by age and tissue*

Age	Heart			Pancreas			Adrenal			Liver			Testis		
	Cases	Warthin lesions found		Cases	Warthin lesions found		Cases	Warthin lesions found		Cases	Warthin lesions found		Cases	Warthin lesions found	
		Number	Percent		Number	Percent		Number	Percent		Number	Percent		Number	Percent
20–29	8	0	...	6	0	.	6	0	..	5	0	... ..	3	0	
30–39	33	8	24.2	31	14	45.2	30	5	16.7	39	12	30.8	8	1	12 5
40–49	57	18	31.6	45	16	35 6	43	8	18.6	55	14	25.5	19	7	36 8
50–59	62	24	38.7	57	21	36.8	41	15	36.6	59	12	20.3	20	12	60.0
Total under 60	160	50	31.3	139	51	36.7	120	28	23.3	158	38	24.1	50	20	40.0
60–69	55	27	49.1	53	24	45.3	50	24	48.0	56	24	42.9	22	17	77.3
70 and over	24	13	54.2	19	9	47.4	16	8	50.0	23	8	34.8	9	7	77.8
Total 60 and over	79	40	50.6	72	33	45.8	66	32	48.5	79	32	40.5	31	24	77.4
All ages	239	90	37.7	211	84	39.8	186	60	32.3	237	70	29.5	81	44	54.3

TABLE 13.—*Number of nonsyphilitic cases examined and number and percent in which Warthin lesions were found, by age and tissue*

Age	Heart			Pancreas			Adrenal			Liver			Testis		
	Cases	Warthin lesions found		Cases	Warthin lesions found		Cases	Warthin lesions found		Cases	Warthin lesions found		Cases	Warthin lesions found	
		Number	Percent		Number	Percent		Number	Percent		Number	Percent		Number	Percent
20–29	66	12	18.2	57	4	7.0	56	5	8.9	61	25	41.0	16	7	43.8
30–39	79	15	19.0	80	17	21.2	77	11	14.3	79	23	29.1	21	5	23.8
40–49	99	34	34.3	93	26	28.0	89	25	28.1	97	28	28.9	28	12	42.9
50–59	148	59	39.9	127	50	39.4	105	30	28.6	141	44	31.2	32	10	31.2
Total under 60	392	120	30.6	357	97	27.2	327	71	21.7	378	120	31.7	97	34	35.1
60–69	109	57	52.3	105	41	39.0	82	24	29.3	109	25	22.9	28	12	42.9
70 and over	111	56	50.5	106	37	34.9	93	35	37.6	116	37	31.9	26	20	76.9
Total 60 and over	220	113	51.4	211	78	37.0	175	59	33.7	225	62	27.6	54	32	59.3
All ages	612	233	38.1	568	175	30.8	502	130	25.9	603	182	30.2	151	66	43.7

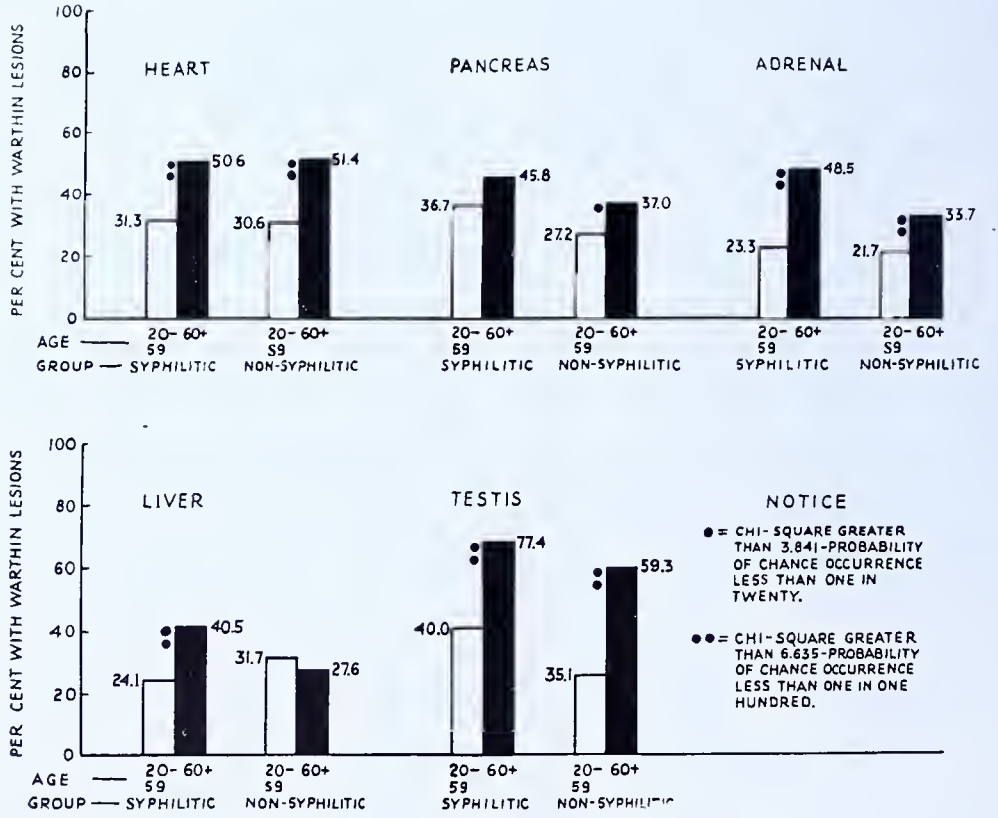

CHART 5.—Incidence of Warthin lesions in syphilitic and nonsyphilitic groups according to age, class, and tissue.

"under 60" class, but the difference was not significant (chi-square = 1.65).

The nonsyphilitic group gave essentially the same results. Here the proportion of persons with Warthin changes in the heart, adrenal, and testis was significally greater in the "60 and over" class than in the "under 60" class (chi-square: heart = 25.74, adrenal = 8.56, testis = 8.26). In the pancreas the difference between the two age classes was in the same direction but only probably significant (chi-square = 4.21). The liver of the nonsyphilitic group was the only organ of those studied which showed a slightly

higher proportion of cases with Warthin lesions in those under 60 than in those over 60, but the difference here was insignificant (chi-square = 1.18).

Cross comparisons between the syphilitic and nonsyphilitic groups in each age class were also made. In the "under 60" class only the pancreas showed a suggestive difference between the proportions of syphilitics and nonsyphilitics with Warthin lesions, the chi-square values for the other 4 organs indicating an absence of significant heterogeneity (chi-square: pancreas = 4.33, heart = 0.02, adrenal = 0.13, liver = 3.17, testis = 0.35). In the "60 and over" age category, the adrenals and liver showed a borderline significant difference in the proportions of syphilitics and nonsyphilitics with Warthin changes, but the two groups were homogeneous as regards Warthin changes in the other three organs (chi-square: adrenal = 4.45, liver = 4.59, heart = 0.01, pancreas = 1.77, testis = 2.89). In not a single one of the 10 comparisons was the value for chi-square greater than 6.635, at which level the probability of chance as a factor accounting for any observed difference is less than 1 in a hundred.

These findings indicate that so far as the syphilis population is concerned, age is related to the incidence of Warthin lesions, more persons with Warthin lesions falling into the older age categories than persons without these changes. With the exception of the liver, the observations on the nonsyphilitic population parallel those on the syphilitic population. This is not to be interpreted as indicating that age is the only factor concerned in the production of the Warthin phenomenon, but it is clearly one variable which must be considered when an explanation for these lesions is sought.

Weller's data on the adrenal, liver, and testis tend to confirm the relation between age and the presence of the Warthin tissue changes. Twenty of eighty-nine persons between 21 and 60 years of age, or 22.5 percent, had these changes in the adrenals, as compared with 14 of 49 persons, or 28.6 percent, of those over 60 years. For the liver, 5 of 89 persons between 21 and 60 years, or 5.6 percent, showed the histologic changes, as compared with 9 of 50 persons in the older age group (18.0 percent). Lesions of the testis showed a similar differential between the older and younger age groups. There were 26 out of 55 persons under 60 years, or 47.3 percent, and 16 out of 23 persons over 60, or 69.6 percent, with these lesions in the testis. The heart findings, however, were different, for here fewer persons with Warthin changes were over 60 than under 60 years of age.

The significance of the aging process in relation to the Warthin lesion of fibrosis and round cell infiltration, in both syphilitic and nonsyphilitic populations, has been demonstrated. Other factors may also be operative, but regardless of what they may be, the evidence does not support Warthin's contention that the microscopic lesion which he described so carefully is pathognomonic of syphilitic infection.

CHAPTER 5

MORTALITY AND MORBIDITY FINDINGS IN THE YALE AUTOPSY SERIES [1]

This chapter will discuss the incidence of the anatomic changes produced by syphilitic infection among individuals aged 20 and over who were observed at necropsy in the Department of Pathology at the Yale University School of Medicine during the period 1917 to 1941. Three groups, controlled by appropriate observations on the nonsyphilitic population, will be considered. These are: (1) those with morphologically demonstrable tissue changes of syphilis, who, in the opinion of the prosector, supported by the judgment of the reviewers, died primarily as a result of these lesions; (2) those with anatomic changes ascribed to syphilitic infection who died primarily from some other disease process; and (3) those with historical or clinical or laboratory evidence of syphilitic infection during life in whom anatomic changes attributable to syphilis could not be demonstrated at autopsy.

In the first chapter it was concluded that the great variability in the incidence of syphilitic changes at autopsy reported by different investigators was largely the result of varying criteria for the morphologic diagnosis of syphilis. A brief statement concerning our own criteria is in order at this time. These autopsies were conducted by many different prosectors associated with the Department during a period of over 20 years. All diagnoses were based upon gross and microscopic examinations and all were checked and confirmed by group discussion among members of the Department at the time of the necropsy. The criteria generally observed were those enunciated by Nickel (*21*), that is, definite anatomic changes of syphilis of the central nervous system, vascular tree, bone, and parenchymatous organs including liver. Presumptive evidence of syphilis such as orchitis fibrosa, lingua glabia, and so-called syphilitic cirrhosis of the liver were not accepted as indicative of morphologic syphilis. Warthin's criteria of lymphocytic and round cell infiltration with fibrosis in liver, heart, adrenals, testes, and pancreas were not followed.

Syphilis Morbidity

A total of 3,907 individuals over 20 years of age was autopsied. Of these, 90 had anatomic lesions of syphilis which were primarily responsible for death, 66 showed anatomic lesions of syphilis but died primarily as the result of some other disease process, and 224 individuals with historical or laboratory or clinical evidence of syphilis had no demonstrable syphilitic lesions at autopsy. The distribution of these 3 groups by sex is shown in table 14. The total, 380, represents 9.7 percent of 3,907 adult autopsies in this series. This, as a matter of fact, is the minimum rather than the maximum incidence of syphilis in the autopsy population, since a certain number of those comprising this population were undoubtedly not included in the syphilitic group because of inadequate or incomplete clinical data. This is especially true of many who died shortly after admission and also of a large number of medical examiner's and coroner's cases brought to the hospital for autopsy.

The 9.7 percent incidence of syphilis in our autopsy group is of especial significance in view of Parran's oft-quoted statement, "Syphilis strikes 1 out of every 10 adults." This conclusion is based upon the exhaustive statistical analysis conducted by Vonderlehr

[1] This chapter is a revision of the article *Studies in Syphilis.* III. *Mortality and Morbidity Findings in the Yale Autopsy Series,* by Paul D. Rosahn and Bernard Black-Schaffer, which appeared in the *Yale Journal of Biology and Medicine,* vol. 15, p. 587, 1943.

TABLE 14.—*Presence or absence of anatomic lesions of syphilis at autopsy in Yale series according to sex*

Group	Male		Female		Total	
	Number	Percent	Number	Percent	Number	Percent
Anatomic lesions causing death	68	25.7	22	19.0	90	23.7
Anatomic lesions not related to cause of death	50	19.0	16	13.8	66	17.4
Total anatomic lesions	118	44.7	38	32.8	156	41.1
No anatomic lesions	146	55.3	78	67.2	224	58.9
Total	264	100.0	116	100.0	380	100.0

and Usilton (*25*), who computed the annual attack rate per 100,000 individuals born alive and followed throughout life. In spite of a comparatively low annual attack rate, they showed that when cumulated so as to indicate the probability of acquiring syphilis by any given age, 10,000 people out of every 100,000 born alive will have acquired syphilis before the age of 50 years has been reached. This method of analysis begins at birth and projects the probability of acquiring syphilis into any given age period in the future. Our own study reverses the process. We have looked back from the vantage point of life's end, that is, from the time of death, and have retrospectively studied the clinical histories of a large autopsy population. Roughly 10 percent of our autopsy population presented clinical or other evidence of syphilis. This finding is identical with the conclusion reached by Vonderlehr and Usilton, and serves as corroborative evidence, reached by a totally different approach, that syphilis attacks 1 out of 10 adults.

Frequency of Anatomic Lesions at Autopsy

From table 14 it is apparent that 156, or 41.1 percent of the 380 syphilitic individuals coming to autopsy had morphologic changes recognized as syphilitic. Melchior (*19*) and Frates (*18*) are the only other authors from whose material corresponding categories could be obtained, and of the two there is internal evidence that Melchior's clinical observations were the more careful. Out of 353 autopsied syphilitics, Melchior found tissue changes of syphilis in 245, or 69.4 percent, while the corresponding finding by Frates is 418, or 82.9 percent, of 504 syphilitics. Summating these findings without regard to variety or intensity of treatment or to criteria for the anatomic diagnosis of syphilis, approximately from one-half to two-thirds of syphilitics show morphologic tissue changes of syphilis at autopsy.

The group of syphilitics with no specific anatomic lesions at autopsy challenges explanation. Was the clinical diagnosis in error? If not, did spontaneous or therapeutic cure, both biologic and morphologic, take place? Did tissue lesions, originally present, completely regress, leaving no residual changes to draw attention to earlier alterations in morphology? Or were tissue changes of a specific nature actually present at autopsy and unrecognized as such?

Each of these questions requires further study, but an interesting side light on them is shown in table 15. The treatment status of 194 of the 224 syphilitics with no lesions at autopsy was known. Of this group, 109, or 56 percent, had received no treatment of any kind. More than half of this untreated group, 63, or 58 percent, were diagnosed as latent syphilitics on their last admission, that is, the only evidence of the disease was serologic positivity. It is apparent then that about half of the syphilitics with no demonstrable lesions at autopsy had never received treatment, and furthermore that a majority of these were diagnosed as syphilitic on the basis of accepted serologic criteria. It should be stated that the necropsy included an examination of the brain in 129 of these 224 individuals. In this group, therefore, tissue changes either did occur and were unrecog-

TABLE 15.—*Clinical status on last admission and history of treatment of 224 syphilitics with no anatomic lesions of syphilis at autopsy*

Status on last admission	Received treatment	Never treated	Treatment not known	Total
Cured	24	10	5	39
Latent syphilis	27	63	11	101
Organic changes clinically diagnosed	23	14	2	39
Syphilis not diagnosed [1]	11	22	12	45
Total	85	109	30	224

[1] This group had a past history of syphilis which was not noted or was overlooked on the last admission.

nized, or regression of lesions took place with or without treatment, or lesions never developed.

Syphilis as a Primary Cause of Death

Ninety out of the one hundred and fifty-six individuals with anatomic lesions at autopsy died primarily as a result of their syphilis (table 14). This is 57.6 percent of the group, or 23.7 percent of the 380 syphilitics and 2.3 percent of the total population of 3,907 individuals (chart 6). Table 16 summarizes the findings of other reporters. Of 2,003 syphilitics with tissue changes, 1,463, or 73 percent, died primarily as the result of the specific infection. This represents 3.6 percent of the total of 39,907 autopsies.

What were the chances of a fatal outcome once a clinical diagnosis of syphilis was made? In our group of 380 syphilitics, there were 320 with historical or clinical or serologic evidence of syphilis. Of this group, 96 had post-mortem changes compatible with a diagnosis of syphilis, and 57 died primarily from their syphilis. Summarizing this experience, once a diagnosis on clinical or laboratory evidence was made, 3 out of 10 syphilitics developed significant tissue lesions, and 1 out of 5 died therefrom. The converse is even more striking, for in 7 out of 10 cases tissue changes did not occur, and in 4 out of 5 syphilis did not cause death. These results do not take into consideration the conditioning influence of treatment, its intensity, or time of initiation.

TABLE 16.—*Syphilis as a primary cause of death in individuals over 20 years of age, according to six reporters*

Author [1]	Column No. 1: Total autopsy population	Column No. 2: Number with anatomic syphilis	Column No. 3: Deaths due primarily to syphilis — Number	Column No. 3: Deaths due primarily to syphilis — Percent of column 2	Column No. 3: Deaths due primarily to syphilis — Percent of column 1
Manohar (*8*)...	2,721	444	323	72.7	11.8
Koppisch (*9*)...	665	76	39	51.3	5.9
Guldberg (*23*)..	8,235	481	349	72.5	4.2
Melchior (*19*)..	4,594	245	140	57.1	2.9
Bell (*10*).....	19,785	601	522	86.9	2.6
Yale series.....	3,907	156	90	57.6	2.3
Total....	39,907	2,003	1,463	73.0	3.6

[1] Figures in parentheses are bibliographic references.

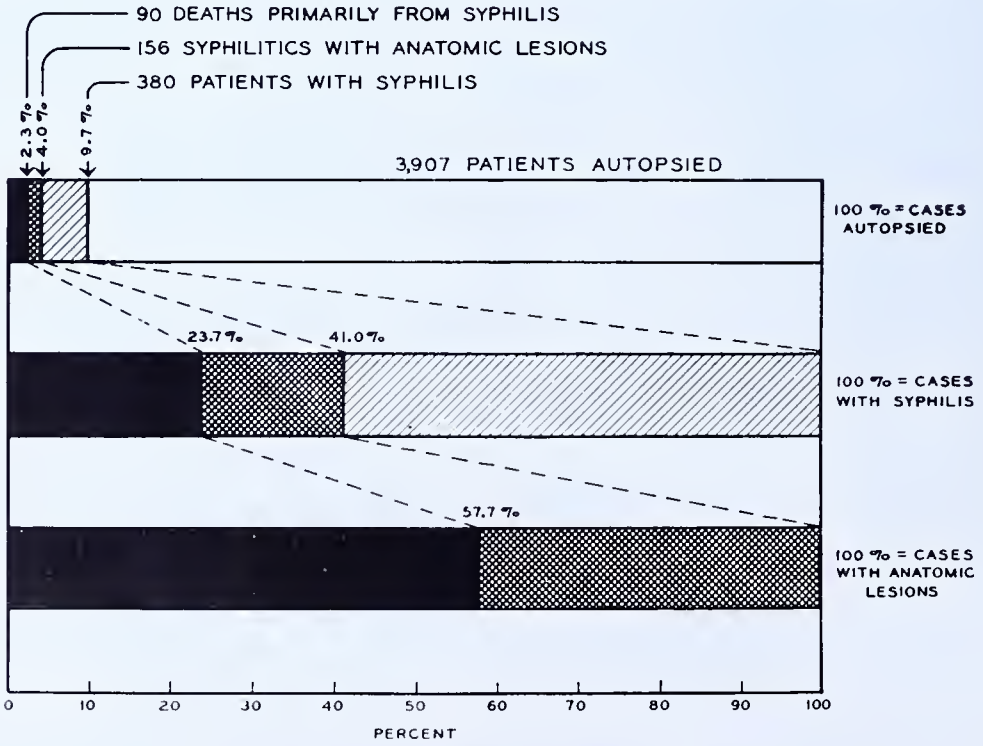

CHART 6.—Proportion of syphilitics, syphilitics with anatomic lesions, and deaths from syphilis in Yale series.

Incidence and Age Distribution of Syphilis in the Negro

Many specialized studies of the pathology of syphilis and a large number of clinical and serologic investigations have been published, but only two papers have been found which give the racial distribution of individuals with anatomic lesions at autopsy. Of necessity, European pathologists have confined their remarks almost exclusively to findings on Caucasians. Ogden (*12*), in New Orleans, found an incidence of 3.9 ± 0.4 percent among whites and 10.5 ± 0.5 percent among Negroes, while Koppisch (9) found 8.6 ± 1.4 percent of his whites and 14.9 ± 2.3 percent of his Negro population with syphilitic lesions at autopsy (table 17). The comparable figures for our own study are 3.3 ± 0.3 percent and 13.8 ± 2.2 percent. Table 17 also indicates the distribution by race of the total autopsy populations studied. Ogden's series included 57.8 percent Negroes, while Koppisch had 38.4 percent Negroes in his series, and our own study was based upon a population comprising 6.3 percent Negroes. In spite of these relatively wide fluctuations in the Negro components of the three series, it is noteworthy that the incidence of syphilis among Negroes in the three studies is essentially the same with an average of 13.1 percent. Giving due weight, however, to the numbers involved in each series, there were 400 Negroes with anatomic lesions of syphilis, or 11.0 percent of a total Negro autopsy population of 3,622.

In contrast to the relatively similar incidence of syphilis found in Negroes in New Orleans, Puerto Rico, and New Haven, there is dissimilarity in the incidence among whites. In this instance the New Haven and New Orleans findings do not differ from each other, but the frequency of anatomic lesions in whites in both of these localities is significantly lower than in Puerto Rico.

Of 97 Negroes in our syphilitic group of 380, 34 individuals, or 35 percent, had anatomic lesions of syphilis (table 18). The comparable figure for the white population of 282 syphilitics was 122, or 43.3 percent. The difference between these two findings is statistically not significant, and it may be concluded therefore that in our series there was no greater frequency of anatomic lesions among syphilitic Negroes than among syphilitic whites. However, in spite of this finding, more whites with anatomic lesions (73 out of 122 cases, or 60 percent) died primarily as the result of their syphilis than did Negroes (17 out of 34 cases, or 50 percent). This is shown in table 18. Although the difference between these values is not statistically significant, the findings are contrary to the generally accepted belief that syphilis runs a more fatal course among Negroes than among whites.

The 97 syphilitic Negroes had a mean age at death of 47.0 ± 1.44 years, in contrast

TABLE 17.—*Syphilitics with anatomic lesions in white and Negro autopsy populations*

Author	White			Negro		
	Total population	Syphilitic		Total population	Syphilitic	
		Number	Percent		Number	Percent
Ogden	2,280	89	3.9±0.4	3,128	329	10.5±0.5
Koppisch	397	34	8.6±1.4	248	37	14.9±2.3
Yale series	3,661	122	3.3±0.3	246	34	13.8±2.2
Total	6,338	245	3.9±0.2	3,622	400	11.0±0.5

TABLE 18.—*Presence or absence of anatomic lesions of syphilis at autopsy in Yale series according to race*

Group	White		Negro		Total	
	No.	Percent	No.	Percent	No.	Percent
Anatomic lesions causing death	73	25.9	17	17.5	90	23.8
Anatomic lesions not related to cause of death	49	17.4	17	17.5	66	17.4
Total anatomic lesions	122	43.3	34	35.0	156	41.2
No anatomic lesions	160	56.7	63	65.0	223	58.8
Total	282	100.0	97	100.0	379	100.0

NOTE: 1 Oriental omitted

to 52.65 ± 0.81 years, the mean age at death of the 282 white syphilitics. These two values are significantly different, indicating that on the average the syphilitic Negro died at a younger age than the syphilitic white. This is in agreement with the general conclusions of Usilton and Miner (*26*), who plotted death curves for white and Negro males with acquired syphilis, utilizing the material of the Cooperative Clinical Group. The same significant differential in mean age was observed when contrasting the nonsyphilitic white populations of control groups A and B with the nonsyphilitic Negro population in the total series of 3,907 cases (chart 7). Moreover, there was no noteworthy difference between the mean age at death of the syphilitics of either race and the mean age of the comparable nonsyphilitic racial groups. From this it appears that in our experience syphilis had no greater influence on Negroes than on whites so far as the mean age at death was concerned, although Negroes, with or without syphilis, died younger than whites.

It has been shown (*27*) that, according to the 1929-31 figures, the life expectancy at birth for Negro males and females is 47.52 years and 49.53 years, respectively, compared to 59.31 and 62.83 years for white males and females. The shorter life expectancy of the Negro has been attributed largely to syphilis. In our own experience cited above, there was no difference between the mean age at death of nonsyphilitics as contrasted with syphilitics, and this was true for Negroes as well as for whites. These figures suggest that the shorter life expectancy of Negroes, both syphilitic and nonsyphilitic, as contrasted to whites, may be due not to the effects of syphilis per se, as has been suggested, but rather to nonspecific factors such as social and economic influences which adversely influence the life expectancy of Negroes in general.

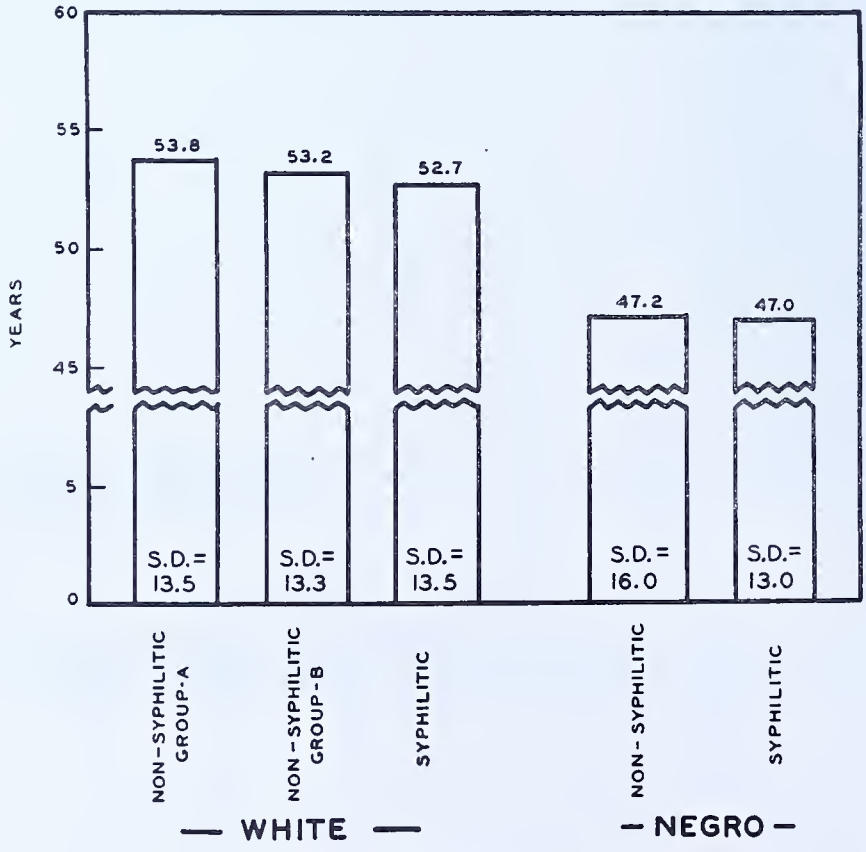

CHART 7.—Mean age and standard deviation of white and Negro syphilitics and nonsyphilitics.

Syphilis and Sex

The 3,907 individuals in our total population were grouped into 2,496 males (63.8 percent) and 1,411 females (36.2 percent). From table 14 it is seen that the 156 syphilitics with anatomic lesions at autopsy consisted of 118 males (75.6 percent) and 38 females (24.4 percent). There were thus significantly more males among the syphilitics with anatomic lesions than there were in our total population (chi-square = 9.38, n = 1, P = < 0.01). In terms of incidence, syphilitic males with lesions constituted 4.7 percent of the male population and syphilitic females with lesions composed 2.7 percent of the female population. These findings are in general similar to those previously reported in a review of the literature and substantiate the general impression that syphilitic lesions at autopsy are twice as frequent in the male as in the female. This might, of course, be explained by a lower rate of exposure or of susceptibility for females than for males. However, when our total group of syphilitics is considered, those with and those without anatomic lesions (table 14), 38 of 116 female syphilitics (32.8 ± 4.4 percent) had anatomic lesions of syphilis at autopsy, as compared with 118 out of 264 males (44.0 ± 3.1 percent). These two rates are probably significantly different (t = 2.1, P = < 0.05), and indicate that anatomic lesions developed less frequently in the female syphilitic than in the male. Thus, even in a group of women diagnosed as syphilitics on clinical or historical or other evidence, syphilitic lesions occurred less frequently than in a comparable group of men. The conclusion seems justified that sex is an important factor in resistance to the tissue changes of syphilis.

This generalization is independent of race, as is shown in table 19. Whites and Negroes in control group A both had an identical sex distribution, that is, 60 percent males and 40 percent females. Similarly white and Negro syphilitics with anatomic lesions also had an identical sex distribution, 75 percent males and 25 percent females. Thus the sex distribution among our syphilitics with lesions at autopsy was essentially identical regardless of race.

TABLE 19.—*Sex distribution by race in control group A and among syphilitics with anatomic lesions of syphilis at autopsy*

Group	Sex	White		Colored		Total
		No	Percent	No	Percent	
Control Group A	Male	216	59.5	10	58.9	226
	Female	147	40.5	7	41.1	154
Total		363	100.0	17	100.0	380
Syphilitics with lesions at autopsy	Male	93	76.3	25	73.6	118
	Female	29	23.7	9	26.4	38
Total		122	100.0	34	100.0	156

Syphilis and Longevity

Since it has been shown in a previous section that Negroes, both syphilitic and nonsyphilitic, die at a significantly earlier mean age than whites, the following analysis deals solely with white individuals. Males and females have been grouped together in order to increase the number of observations.

Table 20 shows the mean age at death of the whites in control groups A and B, and in the syphilis group. The latter has been further broken down into its constituent categories. There is no significant difference between any of the values shown in the table. In our material, therefore, there was no indication that syphilis had any effect on the mean age at death regardless of whether or not it resulted in specific tissue changes, and whether or not it was primarily responsible for death.

TABLE 20.—*Mean age at death of nonsyphilitic and syphilitic white individuals in Yale autopsy population*

Group	Number	Mean age in years
Nonsyphilitic:		
Control A	355	53 9±0 71
Control B	353	53 2±0 71
Syphilitic:		
Without lesions	157	51 5±1 12
With lesions, death primarily from syphilis	70	52 1±0 78
With lesions, death from other cause	49	54 2±1 76
Total	276	52 5±0 81

This generalization is not to be construed as an indication that syphilis has no influence on longevity. The following more detailed

analysis shows that the syphilitic had a shorter life span than the nonsyphilitic, even though no anatomic lesions recognizable as such were found at autopsy (table 21 and chart 8).

The individuals in each group and subgroup were arranged in three age categories: under 40, between 40 and 70, and over 70. As was to be expected from our preliminary analysis, control groups A and B were similarly distributed with respect to these three age classifications.

TABLE 21.—*Age distribution of white syphilitics and nonsyphilitics in Yale autopsy population*

Group	Age in years									Total	
	20–39 9			40–69 9			70+				
	Number	Percent	V [1]	Number	Percent	V [1]	Number	Percent	V [1]	Number	Percent
Nonsyphilitic:											
Control A	86	24.2	5.2	199	56.0	6.9	70	19.7	4.5	355	100.0
Control B	84	23.8	5.1	211	59.8	6.8	58	16.4	3.9	353	100 0
Syphilitic:											
Without lesions	38	24.2	11.7	104	66.2	14.3	15	9.6	5.5	157	100.0
With lesions, death primarily from syphilis	7	10.0	12.9	57	81.4	21.6	6	8.6	11.2	70	100.0
With lesions, death from other cause	7	14.2	24.9	37	75.5	37.8	5	10.2	18.7	49	100 0
Total with lesions	14	11.8	8.7	94	79.0	13.9	11	9.2	7.0	119	100.0
Total syphilitics	52	18.8	5.5	198	71.7	7.4	26	9.4	3.1	276	100.0

[1] Variance $= \sigma^2$

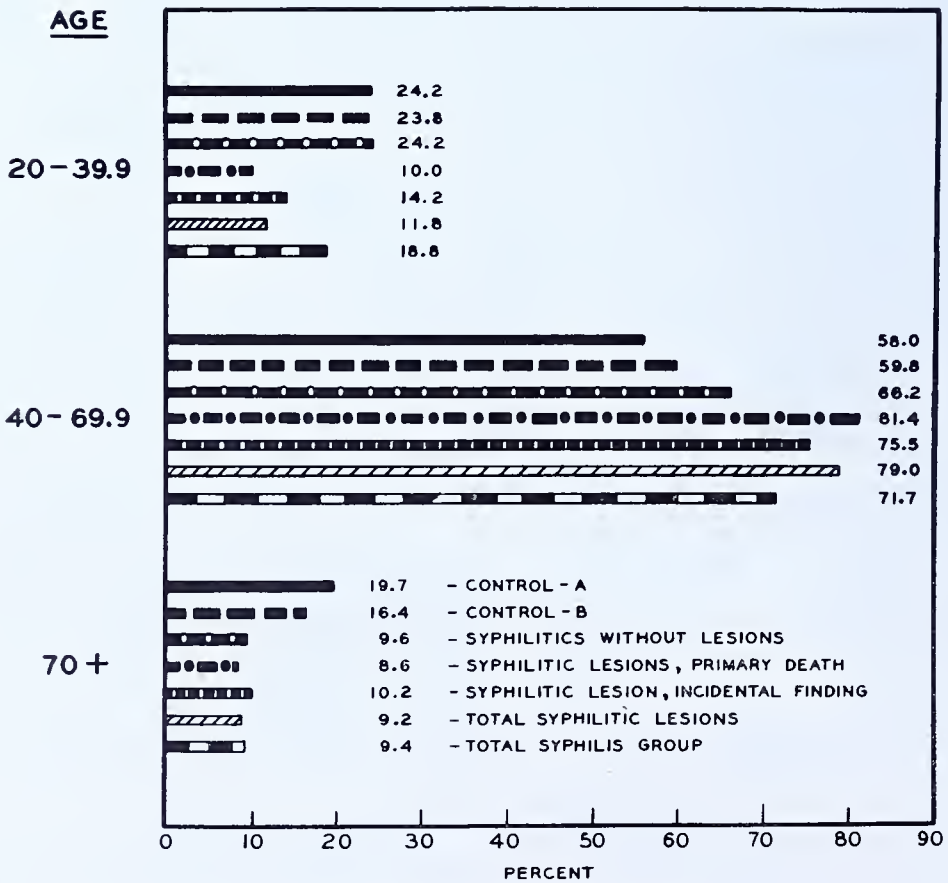

CHART 8.—Age distribution of white syphilitics and nonsyphilitics in Yale autopsy series.

Age 20 to 39.—According to the findings of Vonderlehr and Usilton (*25*), the annual syphilis attack rate per 100,000 persons in 1937 was 1,121 in the age group 20 to 29, and 380 in the age group 30 to 34. Under 20 the attack rate was 299, and over 35 it was 336. The overwhelming majority of primary infections thus occur in the age period 20 to 39. It is generally recognized that a variable number of years must elapse from the time of infection before the tissue changes of late syphilis occur. On this basis one would expect that a group of dead syphilitics with anatomic lesions at autopsy would contain a smaller proportion of individuals in the age group 20 to 39, when most of the primary infections take place, than would be found in a nonsyphilitic population. This expectation is fulfilled by the actual findings. Only 11.8 percent of the deaths among syphilitics with anatomic lesions at autopsy fell into the 20 to 39 year category as compared with the significantly higher values of 24.2 percent and 23.8 percent of the deaths among those comprising the nonsyphilitic populations of control groups A and B. Furthermore, one would expect that the same proportion of a group of syphilitics diagnosed on clinical evidence only, and with no anatomic lesions at autopsy, would succumb in the age group 20 to 39 as in the case of nonsyphilitic persons. This is substantiated by the actual findings, for 24.2 percent of all deaths among the syphilitics who had no recognizable specific lesions at autopsy occurred between 20 and 39, a value which is no different from the comparable values for each of the two control nonsyphilitic populations.

Age 40 to 69.—In the syphilis group the proportion of deaths in the age class 40 to 69 was significantly higher than that observed in either of the two control nonsyphilitic groups. This differential was noted with respect both to the entire group of syphilitics and to the group with anatomic lesions at autopsy. In the case of syphilitics diagnosed clinically and without demonstrable lesions, the proportion dying in this age class was no different from that observed in either control group. More syphilitics succumbed between the ages of 40 and 70 than did nonsyphilitics, although the proportion of syphilitics with no tissue changes and the proportion of nonsyphilitics dying in this age class were no different.

Age over 70.—What proportion of syphilitics and nonsyphilitics lived beyond age 70? There were 19.7 percent and 16.4 percent of control groups A and B in this category in contrast to the significantly lower proportion of 9.4 percent of our total syphilitic group. The break-down by presence or absence of lesions of syphilis is of great interest. It reveals that in our experience, if a syphilitic developed a specific lesion verified by autopsy, and he eventually died primarily as a result of his syphilis, he had the same chances of surviving age 70, about 1 in 10, as the syphilitic with a specific lesion which was not responsible for death. Furthermore, the individual with syphilis, clinically diagnosed and with no anatomic lesion at autopsy, had no greater chance of surviving age 70 than had the syphilitic with demonstrable tissue changes. Each of these syphilitics had about half the chance of the nonsyphilitic of living beyond age 70.

The above findings indicate that syphilis in and of itself definitely reduces longevity. Proportionally more syphilitics with anatomic lesions died between 40 and 69, and fewer survived age 70 than did nonsyphilitics. Only about half as many of the syphilitics who escape tissue changes live beyond age 70 as nonsyphilitics. This latter observation suggests that even though a lesion never develops, or occurs and eventually disappears, the mere fact of infection adversely influences longevity.

Schamberg (*28*) has suggested that our autopsy population contained a number of unrecognized syphilitics who were not included in our syphilis group because of their negative serologic status. Had they been recognized as syphilitic, and included, the disparity between the ratios of nonsyphilitics, and of latent syphilitics in the age group 70 and over would, in Schamberg's opinion, have been equalized. He believes, therefore, that these findings cannot be accepted as indicating that latent syphilis shortens life. The factor mentioned by Schamberg was certainly operative in the selection of our syphilitic group, but it is not possible to estimate the magnitude of its influence on our findings. It is probable, however, that cases of syphilis not included in our syphilis

group because of spontaneous or treatment-induced seronegativity were numerically counterbalanced by cases of latent syphilis who were excluded because their serologic reactions were not studied. As indicated in an earlier chapter, 438 of our original group died at other institutions, and a large majority of these did not have serologic determinations. In addition, 186 died before admission to the New Haven Hospital, and most of these patients had inadequate past histories and laboratory examinations. These 2 groups represent a little more than 10 percent of our total autopsy population, and to them must be added an unknown number of admitted patients who died before serologic tests could be done. We have no way of determining how many seronegative syphilitics were excluded, but by the same token we have no knowledge of the number of seropositive latent syphilitics who were likewise excluded. The 2 groups probably nullified each other.

Evidence from other sources indicates that the disease syphilis does shorten longevity. Smith and M. C. Bruyere (*29*) compared the mortality in a general population with the mortality in that portion of the same population which was known to be syphilitic. Abridged life tables were constructed from available mortality data for whites and Negroes of both sexes. In all four groups considered, the life expectancy of the syphilitic population was lower at every age period than that of the general population. All of the syphilitic persons in this study had received treatment. Heller and P. T. Bruyere (*36*) concluded that the life expectancy of the Negro male between ages 25 and 50, infected with syphilis and untreated, was on the average reduced about 20 percent when compared with nonsyphilitic controls. These two reports, each employing standard statistical methods, emphasize the observation that syphilis, whether treated or untreated, is associated with a reduction in longevity.

A revision of the data appearing in table 4 shows a close parallelism with the Yale material presented in table 21. Table 4, it will be recalled, gives the summated distribution by sex and decennia of the incidence of syphilis in several different autopsy populations. The values for males and females as given in this table have been combined for comparison with our own material, and are presented in table 22. It will be noted that the two series show remarkably close agreement when the age distributions of the two nonsyphilitic populations are contrasted. This agreement is further emphasized by the parallelism observed in the age distribution of the syphilitic groups in both series. The comparative ratios in none of the categories were significantly different. Here again it is seen that although about 20 percent of the nonsyphilitic population survived age 70, less than 10 percent of the syphilitic group in each of the two series lived to age 70 or more. This confirmation of our own findings by the summated experience of five different investigators lends added weight to the conclusion that syphilis decreases longevity.

Several questions immediately come to mind. Does syphilis increase susceptibility to other mortal diseases? Or are syphilitics as a class constitutionally susceptible to other diseases? Or perhaps the environmental influences which contributed to the probability of acquiring syphilis in the first place are also such as to have an adverse influence on longevity? Schamberg (*28*) has recently cited evidence in support of the latter hypothesis.

TABLE 22.—*The age distribution of nonsyphilitic persons and of syphilitic persons with anatomic lesions, in two different autopsy populations*

Group	Source of data	Age in years						Total	
		20–39 9		40–69 9		70+			
		Number	Percent	Number	Percent	Number	Percent	Number	Percent
Nonsyphilitic	Yale series	170	24.0	410	57.9	128	18.1	708	100.0
	Table 4	9,073	23.2	22,699	58.1	7,265	18.7	39,037	100.0
Syphilitic with lesions	Yale series	14	11.8	94	79.0	11	9.2	119	100.0
	Table 4	278	16.4	1,292	76.4	122	7.2	1,692	100.0

CHAPTER 6

THE RELATION BETWEEN BLOOD SEROLOGIC TESTS AND ANATOMIC LESIONS AT AUTOPSY [1]

Major energies in the field of serodiagnosis have been concentrated on technics, evaluation studies, and population surveys, while only minimal efforts have been directed to elucidating the relationship between blood serologic tests and organic lesions of syphilis. It is no doubt of great value to ascertain that a certain proportion of a given population has serologic positivity when tested by a technic with known ratings for sensitivity and specificity. Of greater significance, however, is the projection of this information into terms of morbidity and mortality. What proportion of individuals with positive serologic tests as the only indication of infection can be expected to show organic lesions or to develop them in the future, and what is the probability that these changes will be primarily responsible for death? Furthermore, what proportion of those with a clinical history of syphilis and negative serologic tests can be expected to harbor the infection and to die therefrom? When serologic reversal has occurred, either spontaneously or following specific therapy, what is the expectation that organic lesions, if present, will completely regress leaving no evidence of their previous existence? When serologic reversal does not take place in spite of persistent therapy, what is the probability that organic lesions will persist and cause incapacitating illness and death?

These are problems of far-reaching importance in the interpretation of serologic data, but they have received little attention in the past. They can be approached primarily through retrospective studies of autopsy data, and this report represents such an approach. It is unfortunate that many aspects of the general problem cannot be clarified by our basic observations, which are limited in numbers, but certain generalizations from our data are nevertheless tenable. These will be emphasized in subsequent paragraphs.

During the entire period of this survey all serologic examinations on patients admitted to the New Haven Hospital were carried out in a central serologic laboratory under the supervision of the Department of Immunology. Prior to 1925 the tests were performed by graduate students; since 1925 salaried technicians have been employed. A modified Kolmer complement-fixation test has been the standard procedure. In 1928 the Kahn precipitation test became routine, checked where indicated by the complement-fixation test. The Kline exclusion and diagnostic tests have been used on occasion.

This review is not concerned with the evaluation of serologic performance and the results are not intended to champion any test or tests. For this reason the data have been analyzed without regard to particular serologic procedures. Cases have been classified as serologically positive when any one test has been positive even though one or more other serologic procedures during the same admission were negative.

The Relation Between Serologic Tests and Anatomic Lesions

Table 23 is an association table showing the relation between positive and negative serologic tests in syphilitic individuals with and without anatomic lesions at autopsy. It summarizes the serologic determinations during the last admission of each of the 380 individuals comprising our material. In all subsequent discussions the 4 "doubtful" cases

[1]This chapter revises the article *Studies in Syphilis. IV. The Relation Between Blood Serologic Tests and Anatomic Lesions at Autopsy*, by Bernard Black-Schaffer and Paul D. Rosahn, which was published in the *American Journal of Syphilis, Gonorrhea & Venereal Diseases*, vol. 28, p. 27, 1944.

TABLE 23.—*The serologic results of 380 syphilitics related to the presence or absence of anatomic lesions at autopsy*

Serologic results	Anatomic lesions at autopsy					
	Number			Percent		
	Present	Absent	Total	Present	Absent	Total
Positive	87	110	197	44.2	55.8	100.0
Negative ...	31	85	116	26.7	73.3	100.0
Subtotal ..	118	195	313	37.7	62.3	100.0
Doubtful ...	3	1	4	75.0	25.0	100.0
Not known.	35	28	63	55.6	44.4	100.0
Total...	156	224	380	41.1	58.9	100.0

are excluded from consideration. Of the 63 individuals with no reported serologic studies, 19 were positive, 7 were negative, and 1 was doubtful on examination of blood obtained post mortem. Thus 36 of our group of 380 had no serologic examination on their last admission or at necropsy.

It is noteworthy that all evaluation studies give higher ratings for specificity than for sensitivity. Sensitivity may be defined as the ability of a test to detect the presence of the reacting substance in the serums of known syphilitics; and specificity may be said to indicate the ability to exclude the presence of reagin in the serums of presumably nonsyphilitic donors. In many instances tests have been 100 percent specific, while a rating of 90 percent or more for sensitivity is exceptionally fine. In other words, false negative reports are much more frequent than false positive findings. In spite of this it is more usual for physicians to request confirmatory tests when a positive report is rendered than when a negative finding is reported.

The frequency of post-mortem lesions in individuals with ante-mortem positive serologic tests was significantly greater than in syphilitics with ante-mortem negative tests. Of 197 individuals with positive blood tests, 87 (44.2 $\pm$ 3.54 percent) had anatomic lesions, while of 116 syphilitic patients with negative serologic tests, 31 (26.7 $\pm$ 4.11 percent) had lesions. The difference between these values is significant (D = 17.4 $\pm$ 5.42, t = 3.2; chi-square = 9.4528, n = 1, P = 0.0021). It is noteworthy, however, that among those whose ante-mortem serologic tests were unknown or doubtful, the proportion of post-mortem lesions found was significantly higher than among those whose blood tests were known, and that in actual percentages this unknown group had by far the highest proportion of lesions. This is probably because many of the individuals in this group were selected by the very fact that lesions were present at autopsy.

The Serologic Tests of Individuals with Anatomic Lesions

Table 24 summates the serologic findings in 826 individuals who presented anatomic lesions of syphilis at autopsy on the basis of criteria acceptable to the different reporters.

TABLE 24.—*The serologic tests of individuals with anatomic lesions of syphilis at autopsy according to various authors*

Author	Serologic results					
	Number			Percent		
	Positive	Negative	Total	Positive	Negative	Total
Yale series..	87	31	118	73.7	26.3	100.0
Brines (*31*).	321	82	403	79.7	20.3	100.0
Melchior (*19*)	82	31	113	72.6	27.4	100.0
Symmers (*11*)	46	21	67	68.7	31.3	100.0
Teodori (*17*)	103	22	125	82.4	17.6	100.0
Total...	639	187	826	77.4	22.6	100.0

[1] Figures in parentheses are bibliographic references

It should be remembered that there exists no uniformity as regards serologic procedures or criteria of anatomic changes of syphilis as between the several investigators. The Yale material and Melchior's (*19*) contribution are based on individuals aged 20 and over. Teodori's (*17*) findings do not include neonatal syphilitics, nor individuals with negative serologic tests and a history of antisyphilitic therapy in the recent past. This latter procedure obviously gives increased weight to the group with positive serologic tests. The ages of Symmers' (*11*) and Brines' (*31*) cases do not appear in their original reports. However, congenital syphilitics were excluded from Symmers' findings as far as practicable, and from internal evidence it is fair to assume that only an insignificant fraction of Brines' autopsy population of syphilitics represents neonatal infections. Brines' observations include 21 individuals with doubtful serologic reports, and our own material has 3 cases in this category; these have been excluded from the table. In spite of variations

in technics and criteria it is seen that approximately one-quarter of these individuals with anatomic lesions at autopsy were reported to have been serologically negative. This is not to be interpreted as indicating persistent negativity, for it is entirely reasonable to assume that serologic positivity might have been discovered in many of these individuals had they been tested on other occasions. In this connection, it is of interest that 7 of our 31 patients with negative serologic tests on their last admission and anatomic lesions of syphilis at autopsy are known to have been serologically positive on a previous occasion. However, the findings do suggest that a spot survey of individuals with anatomic lesions of syphilis, without regard to duration of infection, types of lesions, or kinds or amounts of treatment, will disclose serologic negativity in about one-fourth of the group. Even though an anatomically demonstrable syphilitic lesion is present, the blood serums of these individuals do not react positively to the usual serologic tests for syphilis.

The explanation for this phenomenon is not readily apparent. Possible variables which may have some relation to it are: duration of infection; anatomic distribution of lesions; the presence of single or multiple systemic disease; and treatment status. Each of these will be considered separately by comparing the negative serologic group with the positive group, both groups having syphilitic lesions at autopsy.

Variables Which May be Responsible for Serologic Negativity in the Presence of Anatomic Lesions of Syphilis

Duration of Infection

Information concerning the duration of infection was available for only 8 of the 31 individuals with negative serologic tests, and for 24 of the 87 with positive tests. Six of the 8 in the first group, and 20 of the 24 in the second had had their infections for more than 15 years. There is no significant difference between these values, although the observations are admittedly too few for final conclusions.

Anatomic Distribution of Lesions

The distribution of the anatomic lesions in the 118 patients with anatomic lesions and known serologic tests is shown in table 25.

TABLE 25. — *Systemic distribution of anatomic lesions at autopsy in individuals with positive and negative serologic tests on their last admission*

System	Serologic tests		
	Positive	Negative	Total
Cardiovascular	72	26	98
Central nervous	17	4	21
Liver	8	2	10
Other	4	1	5
Total	[1] 101	[2] 33	134

[1] 87 different patients.
[2] 31 different patients.

The incidence of cardiovascular disease in this group was 83.1 percent; of central nervous system syphilis, 17.8 percent; and of liver syphilis, 8.5 percent. The comparable figures reported by Brines are 71.4 percent, 30.6 percent, and 6.2 percent. In our group of 31 patients with negative serologic tests, 26 (83.9 percent) had cardiovascular syphilis; 4 (12.9 percent) had syphilis of the central nervous system; and 2 (6.5 percent) showed liver changes of syphilis. In comparison with these findings, 72 (82.8 percent) of 87 patients with positive serologic tests had cardiovascular syphilis; 17 (19.5 percent) had central nervous system syphilis; and 8 (9.2 percent) had syphilitic livers. There is no significant difference between the negative and positive serologic groups as regards the distribution of anatomic lesions, and it is not possible, therefore, to explain on this basis the negative serologic results in individuals with anatomic lesions.

Syphilis of One or of More Than One System

Brines has reported that individuals with lesions in more than one organ had a higher incidence of positive serologic tests than those in whom only one organ was the locus of syphilitic disease. Our own data have been analyzed by system rather than by organ. The positive serologic group of 87 included 14 (16.1 percent) with lesions in more than one system, as contrasted with 2 individuals

(6.5 percent) in our group of 31 with negative serologic tests. Although these values appear to confirm Brines' findings, the difference between them is statistically not significant. However, the results are suggestive, and further observations on this aspect of the problem seem warranted.

Treatment

The treatment status is known of 75 of our 87 patients with positive serologic tests and anatomic lesions at autopsy. There were 57 patients in this group (76 percent) who had never received any specific therapy. Our negative serologic group of 31 included 25 whose treatment status was recorded. Of this group 18 (72 percent) were never treated. The two groups are thus no different from each other so far as therapy is concerned.

In summary of the above discussion, we have no indication that duration of infection, system or systems involved, or therapy was individually responsible for negative serologic tests in the presence of an anatomic lesion of syphilis. There is suggestive evidence that when a single system is involved, the serologic results are more likely to be negative than when more than one organ system is the site of syphilitic change. Final conclusions on any of these factors should not be drawn, however, because of the limited number of observations.

Scott (*32*) has suggested that perhaps the negative serologic results in syphilitics with anatomic lesions were in large measure a reflection of the insensitive serologic technics employed in the early years of this autopsy series. The material has been analyzed with this possibility in mind. Of the 118 syphilitics with anatomic lesions, 38 were autopsied in the period 1917 to 1927, and 80 between 1928 and 1941. Seven of the former group, or 18.4 percent, were serologically negative on their last admission, as contrasted with 24, or 30 percent of those autopsied in the later time period. These two values are not significantly different, although the direction and magnitude of their difference tend to substantiate Scott's hypothesis. With the limited number of observations available for analysis, however, it can be concluded that the frequency of negative serologic results in the presence of anatomic lesions of syphilis was not significantly influenced by any lack of sensitivity that might have existed in the early serologic procedures.

Anatomic Lesions in Individuals with Positive Serologic Tests

In table 26 is shown the presence or absence of anatomic lesions of syphilis in individuals with ante-mortem positive serologic tests. Four individuals with doubtful tests in our material have been excluded. With one exception, Melchior, all of the reporters find an approximately equal division into those with and those without specific anatomic changes. The reasons for the disparity between Melchior's observations and those of the others are not readily apparent. The summated total, however, indicates that 223 individuals (46.8 percent) of the 476 with positive serologic tests revealed no anatomic changes at autopsy consistent with a diagnosis of syphilis. The conclusion is inevitable that the toss of a coin would have been as effective in indicating which of the cases would show anatomic evidence of their disease. Serologic positivity in and of itself is thus uncertain evidence of the tissue changes of syphilis as determined by autopsy examination.

TABLE 26.—*The presence or absence of anatomic lesions at autopsy in individuals with positive serologic tests, according to various authors*

Author	Anatomic lesions at autopsy					
	Number			Percent		
	Present	Absent	Total	Present	Absent	Total
Yale series	87	110	197	44.2	55.8	100.0
Brines	39	45	84	46.4	53.6	100.0
Melchior	82	17	99	82.8	17.2	100.0
Symmers	45	51	96	46.9	53.1	100.0
Total	253	223	476	53.2	46.8	100.0

Variables Which May Be Responsible for Serologic Positivity in the Absence of Anatomic Lesions of Syphilis

There are at least two factors which may account for the absence of anatomic lesions in individuals with positive serologic tests. These are duration of infection, and therapy.

Duration of Infection

This was known for 24 of our 87 patients with positive serologic results and anatomic lesions. Infection was known to have been present for more than 15 years in 20 of these individuals. In contrast to these findings, of 16 patients with positive serologic tests and no anatomic lesions at autopsy, the duration of whose infection was known, 10 had evidence of the disease for more than 15 years. There is no significant difference between these two groups so far as duration of infection is concerned.

Specific Therapy

We have information concerning the therapy received by 75 of the 87 patients with positive serologic tests and anatomic lesions at autopsy, and by 90 of the 110 individuals with positive tests and no anatomic lesions. In the first group mentioned, 57 (76.0 percent) never received any treatment, compared to 72 (80.0 percent) in the second group. Here again there is no significant difference between the two series. It is noteworthy that approximately three-quarters of our cases with positive serologic tests never received specific therapy of any kind.

Relation Between Clinical Status and Lesions at Autopsy in Individuals with Positive Serologic Tests

There were 197 individuals with antemortem positively reacting serums in our series of 380 syphilitics. These were grouped in two distinct clinical categories as shown in table 27. The first consisted of those with latent syphilis, a positive serologic result being the only clinical evidence of the disease. The second group comprised individuals with clinically diagnosed anatomic lesions, usually of the cardiovascular or central nervous systems. A clinical diagnosis of an anatomic lesion was made in 62 of 87 individuals (71.3 percent) with demonstrable tissue changes at autopsy, and in 18, or 16.4 percent, of 110 individuals with no morphologic lesions at autopsy. The difference between these values is highly significant. Thus among patients with anatomic lesions at autopsy, the clinical diagnosis of organic disease was made more frequently than among patients with no autopsy changes. Analysis of table 27 along the horizontal rows instead of the vertical rows, shows that 62 of 80 patients (77.5 percent) in whom a clinical diagnosis of organic lesions was made, had anatomic changes at autopsy, as compared with only 25 of 117 patients (21.4 percent) who were diagnosed clinically as latent syphilitics. Seven of these 25 patients incorrectly diagnosed as latent syphilitics died as a direct result of syphilitic lesions. This is 6.0 percent of the 117 cases of clinically diagnosed latent syphilis.

TABLE 27.—*The clinical status on the last admission of 197 individuals with positive serologic tests, related to the presence or absence of anatomic lesions at autopsy*

Clinical status	Anatomic lesions					
	Number			Percent		
	Present	Absent	Total	Present	Absent	Total
Latent—no clinically apparent organic lesions	25	92	117	28.7	83.6	59.4
Organic lesions clinically diagnosed....	62	18	80	71.3	16.4	40.6
Total..	87	110	197	100.0	100.0	100.0

A comparison of these results with those of the previous section indicates the value of clinical study in determining the significance of a positive serum. When the only information available about a patient was the fact that his serum was positive, the probability that he had an anatomic lesion was about 50 percent. If, however, to this knowledge was added that derived through clinical examination, the chances of correctly diagnosing an anatomic lesion were increased to about 75 percent. A clinical appraisal thus brought the probability of correctly diagnosing an organic lesion out of the realm of coin-tossing. It should be pointed out that the above analysis does not deal with the accuracy of the clinical diagnosis of organic syphilitic disease, but rather is concerned with the confirmation of the clinical diagnosis of an anatomic lesion by the presence of any syphilitic lesion at autopsy.

Relation Between Clinical Status and Lesions at Autopsy in Syphilitic Individuals with Negative Serologic Tests

Table 28 summarizes the clinical status of 116 syphilitic individuals with negative serologic tests on their last admission in relation to the presence or absence of anatomic lesions at autopsy. In this group were 43 patients who on clinical grounds were believed to have been cured; at autopsy, lesions were found in 5 (11.6 ± 4.87 percent). Of 29 patients who on clinical grounds were believed to have an organic syphilitic lesion, 8 were found at autopsy to have morphologic tissue changes of syphilis. In this instance the ante-mortem diagnosis was correct in 27.6 ± 8.3 percent. The difference between these two values is not significant. Lesions were found at autopsy just as often in those clinically diagnosed "cured" as in those clinically diagnosed "organic disease." The conclusion appears warranted that, given a syphilitic individual with negative serologic tests, a clinical evaluation leading to the specifically stated impression of "no anatomic lesion" or "cured" was likely to be no more accurate when checked with findings at autopsy than a clinical diagnosis of organic disease.

It will be noted that table 28 includes a third category of patients classified on clinical evidence, the "undiagnosed." These comprised 44 of our 116 syphilitic patients (37.9 percent) with negative serologic tests. Five of this group had a previous history of a positively reacting serum which was either ignored or overlooked by the examining physician, 17 had anatomic lesions at autopsy which were not diagnosed clinically, and 22 had significant anamneses or other evidence which justified their inclusion in the group of syphilitics. This procedure merits further explanation. In 5 of these 22 patients the postmortem serologic tests were strongly positive, one other had a positive complement-fixation test on the spinal fluid, not emphasized in the clinical appraisal, and 16 gave a story of primary lesions which clinically were either ignored or overlooked. Only one of these 16 received treatment, while the remaining 15 patients represent those included in the syphilis group solely on the basis of a history of a primary lesion. Herein may lie a source of error, for proof is lacking that the genital sore mentioned by these 15 patients in their anamneses was actually a syphilitic lesion. If it were, healing without residual tissue damage occurred in the absence of specific therapy.

The conclusion that, among syphilitics with negative serologic tests, the clinical diagnosis of latency was no more accurate than the clinical impression of organic involvement is of interest when compared with the findings on patients with positive blood tests. The clinical impression of no anatomic lesion in the presence of positive tests was correct in 92 of 117 cases (78.6 percent), while a similar impression in the presence of negative serologic tests was correct in 64 of 87 cases (73.6 percent). These values do not differ from each other. In contrast to this agreement are the findings among individuals in whom a clinical diagnosis of organic involvement was made. In this instance the diagnosis was correct in 62 of 80 cases with positive serologic tests (77.5 percent), as compared

TABLE 28.—*The clinical status on the last admission of 116 syphilitics with negative serologic tests, related to the presence or absence of anatomic lesions at autopsy*

Clinical status	Anatomic lesions at autopsy						Total
	Present			Absent			
	Serologic test negative but previously positive	Serologic test negative	Subtotal	Serologic test negative but previously positive	Serologic test negative	Subtotal	
Cured	3	2	5	22	16	38	43
Organic disease clinically diagnosed	3	5	8	10	11	21	29
Syphilis not diagnosed	1	17	18	4	22	26	44
Total	7	24	31	36	49	85	116

with a confirmed clinical diagnosis in 8 of 29 patients with negative blood tests (27.6 percent). These latter values are significantly different. They indicate that when a clinical diagnosis of organic lesions had been made, anatomic confirmation at autopsy was found more often when the serologic test was positive than when it was negative, but when a clinical diagnosis of no organic involvement was recorded, autopsy lesions were found just as often among those whose tests were negative as among those whose tests were positive.

It is apparent that more than usual clinical scrutiny must be followed before making a clinical diagnosis of an organic lesion in the presence of a negative serologic test for syphilis. This is shown by the fact that among those having positive tests, autopsy lesions were found in 62 of 80 (77.5 percent) in whom the diagnosis was made clinically, but lesions at autopsy were noted in only 25 of 117 (21.4 percent) in whom the clinical diagnosis of organic lesions was not made. The difference between these is significant and chi-square equals 60.7098. On the other hand, among those with negative blood tests before death, autopsy lesions were found just as often when the clinical diagnosis had not been made as when it had, the former percentage being 11.6 (5 out of 43) and the latter 27.6 (8 out of 29). Chi-square in this case is 2.9811, which is not significant.

Incidence of Positive Serologic Tests in Syphilitics Dying Primarily of Syphilis and in Those with Syphilitic Organic Disease An Incidental Finding at Autopsy

Of 66 individuals who died primarily of syphilitic organic disease 54 (81.8 $\pm$ 4.87 percent) had positive ante-mortem serums while the balance had negative blood tests. There were 52 patients in whom syphilitic organic disease was observed at autopsy as only an incidental finding unrelated to the cause of death. Of this group, 33 (63.5 $\pm$ 6.68 percent) had positive serums ante mortem. The difference between these two groups is probably significant ($D = 18.3 \pm 8.26$, $t = 2.21$, $P < 0.05$). A previous section has indicated that the frequency of positive serologic tests among 195 individuals with historical or other evidence of syphilis but with no anatomic changes produced by the disease was 110 or 56.4 $\pm$ 3.55 percent. This is statistically no different from the above-indicated 63.5 percent frequency of positive serums in syphilitics with incidental organic lesions unrelated to the cause of death, but has a highly significant difference from the 81.8 percent incidence of positive serologic tests in individuals dying primarily from syphilitic organic disease. ($D = 25.4 \pm 6.02$, $t = 4.21$, $P < 0.01$). However, of the three groups, the one in which syphilitic lesions were primarily responsible for death had the highest incidence and the group with no lesions had the lowest incidence of positive blood tests. This suggests that there is an increasing proportion of positive serologic tests with increasing activity of the disease.

Syphilis as a Primary Cause of Death in Syphilitics with Positive and Negative Serologic Tests

There were 197 individuals with positive serologic tests in our series. Syphilitic organic lesions were primarily responsible for the death of 54 of these, a frequency of 27.4 $\pm$ 3.17 percent. In contrast to this finding, 12 individuals in our group of 116 with negative serologic tests died primarily as a result of the morphologic tissue changes of syphilis, a rate of 10.3 $\pm$ 2.82 percent. The difference between these two values is highly significant. In general terms, about 1 out of 4 syphilitics with positive serologic tests, and about 1 out of 10 syphilitics with negative tests, died primarily as a result of their infection. The likelihood of syphilis being the primary cause of death was more than twice as great in individuals with positive blood tests as in syphilitics with negative serums.

Serologic Reversal in Relation to Anatomic Lesions

Forty-three individuals whose serologic tests were negative on their last admission were known to have had a previously positive serum. This represents 37.1 percent of all the negative reactions. Anatomic lesions were observed in 7 of the 43, or 16.3 percent. Four of these were males and 3 were females. Of the males, only 1 had not been treated, and

this person died primarily of syphilitic disease. Of the females, 2 had received no treatment and none died as a direct result of syphilis. Anatomic lesions were completely absent in 36 individuals, 15 males and 21 females. Of the males without anatomic lesions, 6 never received treatment, and of the females, 8 were not treated. These observations are admittedly too few for generalizations, but they appear to indicate that neither of the two variables, sex or therapy, was a factor which could account for the presence or absence of anatomic lesions at autopsy in individuals with serologic reversal. More reliance can be placed on the finding that anatomic changes were noted at autopsy in about 1 out of 6 such cases. Of doubtful value is the observation that 1 out of 43 individuals with serologic reversal died directly as a result of syphilitic tissue changes.

Sex, Serologic Tests, and Anatomic Lesions of Syphilis

In table 29 is shown the distribution by sex and serologic results of 118 persons with anatomic lesions at autopsy. It is evident that an equal proportion, approximately three-quarters, of both males and females with anatomic lesions had positively reacting serums. Tables 30 and 31 classify all cases

TABLE 29.—*The sex and serologic results of individuals with anatomic lesions of syphilis at autopsy*

Sex	Serologic results					
	Number			Percent		
	Positive	Negative	Total	Positive	Negative	Total
Male	66	23	89	74.2	25.8	100.0
Female	21	8	29	72.4	27.6	100.0
Total	87	31	118	73.7	26.3	100.0

with positive and negative serologic tests according to sex and syphilitic lesions as a primary cause of death, as an incidental finding, or as absent at autopsy. Neither in the group with positive serologic tests nor in that with negative tests is there any significant difference between the sexes as regards any of these categories. Of the 197 cases with positive tests, 136 (69.0 percent) were males, compared with 78 males (67.2 percent) of 116 syphilitics with negative blood

TABLE 30.—*The sex and primary cause of death in syphilitic individuals with positive serologic tests*

Primary cause of death	Sex					
	Number			Percent		
	Male	Female	Total	Male	Female	Total
Syphilis	40	14	54	29.4	23.0	27.4
Other than syphilis, but syphilitic lesions found at autopsy	25	8	33	18.4	13.1	16.8
Other than syphilis, and syphilitic lesions not found at autopsy	71	39	110	52.2	63.9	55.8
Total	136	61	197	100.0	100.0	100.0

tests. These values likewise are not significantly different. It appears, therefore, that sex did not influence the incidence of positive or negative serologic tests among individuals with anatomic lesions at autopsy, or the frequency of syphilitic lesions as a primary cause of death among syphilitics with positive or negative blood tests. This homogeneity between the sexes suggests that the observations and conclusions in the earlier sections of this report apply with equal merit both to males and to females.

TABLE 31.—*The sex and primary cause of death in syphilitic individuals with negative serologic tests*

Primary cause of death	Sex					
	Number			Percent		
	Male	Female	Total	Male	Female	Total
Syphilis	8	4	12	10.3	10.5	10.3
Other than syphilis, but syphilitic lesions found at autopsy	15	4	19	19.2	10.5	16.4
Other than syphilis, and syphilitic lesions not found at autopsy	55	30	85	70.5	79.0	73.3
Total	78	38	116	100.0	100.0	100.0

Anatomic Lesions in Treated Syphilitics with Positive Serologic Tests

The 197 syphilitics with positive serologic results on their last admission included 36 patients who had received variable amounts of arsenicals during the course of their

disease. In spite of this therapy, serologic reversal failed to take place, as indicated by their positively reacting serums on their last hospital admission. Eighteen of this group (50 percent) had anatomic lesions of syphilis at autopsy, and 9, or one-quarter, died primarily as a result of these lesions. The series is obviously too small for generalizations and none will be attempted.

General Discussion

The findings reported herein should be interpreted in the light of three basic considerations. In the first place a discussion of the relation between any variable, blood serologic tests in this instance, and anatomic tissue changes of syphilis at autopsy, should be prefaced by a clear statement of the criteria followed in diagnosing tissue alteration as evidence of syphilitic disease. Such a statement was given in a previous chapter and merits repetition here: "All diagnoses were based upon gross and microscopic examinations and all were checked and confirmed by group discussion among members of the Department at the time of the necropsy. The criteria generally observed were those enunciated by Nickel (*21*), that is, definite anatomic changes of syphilis of the central nervous system, vascular tree, bone, and parenchymatous organs including liver. Presumptive evidence of syphilis such as orchitis fibrosa, lingua glabia, and so-called syphilitic cirrhosis of the liver were not accepted as indicative of morphologic syphilis. Warthin's (*5*) criteria of lymphocytic and round cell infiltration in liver, heart, adrenals, testes, and pancreas were not followed."

Secondly, our basic data are incomplete because an examination of the central nervous system was not conducted in every case. This is a particularly serious deficiency, especially with regard to the 195 cases with known serologic tests and no anatomic evidence of syphilis. Of this group, 123 (63.1 percent) had an examination of the brain or spinal cord or both at necropsy. The presence or absence of morphologic changes in the central nervous system of the remaining 72 is not known, and to this extent our conclusions must be viewed with caution.

The third factor which must be kept in mind in the interpretation of our data is concerned with the size of our sample. In any statistical study such as ours, where relatively small samples are employed, the demonstration of statistically significant differences between compared groups is much more reliable than the demonstration that compared groups are homogeneous. Especial caution must be exercised in drawing conclusions from samples which are obviously too small and therefore may not be representative of the population from which they were drawn. For this reason the present study is of limited value as regards such special aspects of the general problem as the role of therapy, or the frequency of anatomic changes of syphilis in cases of serologic reversal, or in treated syphilitics with persistently positive blood tests. Moreover, our observations are too few to permit of break-down into age and sex and race categories. Only the accumulated and pooled experience of several institutions comparable to our own will provide sufficient material for acceptable generalizations on such problems.

FIBROSIS AND ROUND CELL INFILTRATION OF THE PARENCHYMATOUS ORGANS (WARTHIN) IN RELATION TO SERODIAGNOSTIC FINDINGS [1]

The tissue changes which Warthin believed were pathognomonic of syphilitic infection have been discussed in chapter 4. In pursuance of the general problem of the specificity of these lesions, it appeared advisable to study their relation to the results of serologic tests for syphilis.

Material and Methods

The comparisons to be presented are between two groups, one composed of individuals with positive serums, and the other of syphilitic persons with negative serums. Table 32 gives the sex distribution of the two groups according to the presence or absence of anatomic lesions of syphilis at autopsy. Each of the 61 individuals with seronegative reactions in whom anatomic lesions of syphilis were absent at autopsy was diagnosed as syphilitic on good clinical or historical evidence, and 22 (36.1 percent) were known to have reacted positively to an earlier serologic test for syphilis. All were white persons, 20 years of age or older. A detailed description of the microscopic technic and of the tissue alterations denoted "Warthin lesions" has been presented in chapter 4.

TABLE 32.—*Distribution of 225 syphilitic patients according to sex, serologic status, and presence or absence of anatomic lesions of syphilis at autopsy*

Serologic test for syphilis	Anatomic lesions present		Anatomic lesions absent		Total
	Male	Female	Male	Female	
Positive	50	17	49	26	142
Negative	19	3	38	23	83
Total	69	20	87	49	225

The serologic tests were performed in a central laboratory, employing technics which have been described in chapter 6. The chi-square test of homogeneity has been utilized in the statistical comparisons, and significance has been attached to values of $P \leq 0.01$.

Results

Table 33 gives the distribution of Warthin lesions according to the organ involved and to serologic classification. In none of the five organs under consideration was the frequency of Warthin lesions in the serologic positive group significantly different from the corresponding frequency of these lesions in the serologic negative group. Thus the serologic results in syphilitic individuals with and without frank anatomic evidence of the disease were not influenced by the tissue changes described by Warthin.

TABLE 33.—*Distribution of Warthin lesions among syphilitic persons with positive and negative serologic reactions, according to organs*

Organ involved	Serologic test for syphilis	Number of cases	Warthin lesion present	Chi-square
Heart	Positive	113	48	3.78
	Negative	71	20	
Pancreas	Positive	102	44	0.42
	Negative	62	30	
Adrenal	Positive	70	24	1.69
	Negative	75	23	
Liver	Positive	119	44	1.24
	Negative	69	20	
Testis	Positive	35	18	0.04
	Negative	26	14	

[1] This chapter revises the article *Studies in Syphilis. VI. Fibrosis and Round Cell Infiltration of the Parenchymatous Organs (Warthin) in Relation to Serodiagnostic Findings*, by Paul D. Rosahn, which was published in the *Journal of Venereal Disease Information*, vol. 27, p. 126, 1946.

In the above analysis, syphilitic persons with and without anatomic lesions of syphilis at autopsy were grouped together. In order to eliminate any possible distortion of the results that might have occurred because of the inclusion in the analysis of syphilitic persons with frank anatomic lesions, a similar analysis was conducted on the group consisting of 136 individuals (see table 32) in whom no evidence of syphilis was discovered post mortem. The results are shown in table 34. Here again the frequency of Warthin lesions in syphilitic individuals with positively reacting serums was organ for organ no different from the frequency of these lesions in those with negative serums.

TABLE 34.—*Distribution of Warthin lesions among syphilitic persons with no anatomic evidence of syphilis at autopsy, according to organs and to serologic reaction*

Organ involved	Serologic test for syphilis	Number of cases	Warthin lesion present	Chi-square
Heart	Positive	57	22	1.51
	Negative	51	14	
Pancreas	Positive	51	25	0.13
	Negative	42	19	
Adrenal	Positive	25	7	0.17
	Negative	60	16	
Liver	Positive	65	27	1.43
	Negative	49	15	
Testis	Positive	15	9	0.02
	Negative	16	10	

The preceding comparisons have to do with the presence or absence of Warthin changes in single organs as related to the results of serodiagnostic tests. An extension of this study was made to determine whether the multiplicity of organs showing Warthin changes could be related to the results of serologic tests for syphilis. For this purpose, the autopsy protocol of each of the 225 syphilitic individuals was reviewed, and a tabulation was made of the number of organs showing the Warthin changes. There were 109 persons in the group with positively reacting serums in whom three or more organs were examined for Warthin changes, as contrasted with 67 persons in the group with negative serodiagnostic findings. Fifty-one of the first group and 31 of the second showed Warthin changes in two or more organs. There is no significant difference between these findings (chi-square = 0.00+). Thus the number of parenchymatous organs showing Warthin changes was not related to the results of serologic tests for syphilis.

On the basis of these comparisons it can be concluded that there is no correlation between the tissue changes described by Warthin, and the reaction of the serum to known tests for syphilis.

CHAPTER 8

THE END RESULTS OF UNTREATED SYPHILIS [1]

The 380 patients with syphilitic disease who were studied at autopsy and who form the basis for this series of reports, received varying amounts of antisyphilitic therapy. Some were well treated by modern standards, others received minimal amounts of treatment, and the third group was untreated. A study of this latter group has presented the opportunity to determine the distribution of morphologic lesions of syphilis in an untreated syphilitic population. This report will present these findings. In only two other series, those of Bruusgaard and of the United States Public Health Service, has there been any attempt to evaluate the clinical and postmortem evidence of syphilis in patients who received no specific therapy for their disease. The work of these investigators is noteworthy and warrants further comment.

In 1929 Bruusgaard (*33*) published a classic report on the fate of syphilitic patients who had received no specific therapy. This study was made on the basis of material which, to quote Bruusgaard's words, "is hardly to be duplicated anywhere else." During the period 1889 to 1910 neither potassium iodide nor mercury was employed in the treatment of early syphilis at C. Boeck's clinic at the University of Oslo. Boeck believed that these drugs do not cure the disease but disturb the healing forces of the body. Consequently the disease becomes atypical and results in serious late lesions, especially of the central nervous system. In the period mentioned, 2,181 patients with primary and secondary syphilis were seen, of whom 1,388 were women and 793 were men. Potassium iodide was occasionally given but never in larger quantities than 100 to 200 grains, and mercury ointments were employed in very few cases. For all practical purposes the group was untreated.

Bruusgaard began his personal interviews of these patients in 1924 and completed them in 1927, including in his study only those patients originally seen from 1891 to 1910. He was able to trace 309 living patients from this group, and these were thoroughly examined clinically. All received a complete neurologic examination and X-ray studies of the heart. In certain instances a spinal fluid examination was performed and almost all patients had a blood Wassermann study. Information about paretics and tabetics was obtained from hospitals and asylums. To this group of 309 living patients there were added 164 patients who had died of known cause, and 40 on whom autopsies had been performed. The findings he presented in a series of tables which have been summarized by Moore (*34*) and by Sowder (*35*), and are presented in somewhat different form in tables 35 and 36. Any discrepancy between the data as presented in these tables and those published by the above-mentioned authors arises from differing classifications of Bruusgaard's published findings. These discrepancies are not serious, however, and do not alter the general conclusions. As indicated in table 36, only 23.0 percent of the entire group presented clinical or autopsy evidence of involvement of the central nervous system, of the cardiovascular system, or died of syphilitic disease. An additional 12.2 percent showed the less serious syphilitic tissue changes in skin or bone. The remaining group, comprising 64.8 percent of the total, either died with no clinical or autopsy evidence of syphilis, or were living from 3 to 40 years after infection with no clinical evidence of the disease. Moreover, 27.9 percent had a negative serologic test and were presumably cured.

[1] This chapter is a revision of the article *Studies in Syphilis.* VII. *The End Results of Untreated Syphilis,* which was published in the *Journal of Venereal Disease Information,* vol. 27, p. 293, 1946.

TABLE 35.—*Duration of syphilitic infection in 473 living and dead patients according to Bruusgaard*

Status of patient at last examination	Duration of infection in years								Total	
	3–10		10–20		20–30		30–40			
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Living	79	25.6	66	21.3	100	32.4	64	20.7	309	100.0
Dead	13	7.9	58	35.4	63	38.4	30	18.3	164	100.0
Total	92	19.4	124	26.2	163	34.5	94	19.9	473	100.0

However, these ratios tend to exaggerate the serious nature of the disease. Sowder (*35*), analyzing Brussgaard's material by several criteria of sampling, demonstrated that it was weighted with cases showing the serious complications of syphilis, and contained too few patients who were symptom-free. Moreover, in the summarized tables presented herewith, many cases are included as syphilitic, even though the original data leave some doubt as to the syphilitic etiology of their disease. As an example of this type of weighting, cases showing "paralysis of the heart," "fatty heart," "arteriosclerosis," "organic heart lesion," and "cerebral apoplexy" are classified in this table as instances of cardiovascular syphilis, while cases of "epilepsy" and "psychosis" are included as central nervous system syphilis. Bruusgaard's observations, the only long-term study of the end results of untreated syphilis, appear to indicate that, in terms of both morbidity and mortality, syphilis is not the dread disease it is commonly believed to be.

TABLE 36.—*Final diagnosis in 473 living and dead syphilitic patients according to Bruusgaard*

Final diagnosis	Living patients	Dead patients	Total	
			Number	Percent
Syphilis of central nervous system	[1] 31	6	[1] 37	7.8
Syphilis of cardiovascular system	[1] 21	48	[1] 69	14.6
Syphilis of skin and bone	58	.... ..	58	12.2
Other syphilitic disease	.....	3	3	.6
No evidence of syphilis, STS+	68	.....	68	14.4
No evidence of syphilis, STS−	132	.....	132	27.9
Cancer	.....	29	29	6.1
Tuberculosis	.....	29	29	6.1
Other disease	.....	49	49	10.3
Total	[1] 310	164	[1] 474	100.0

[1] 1 duplication.

One other study (*30, 36, 37*) under the auspices of the United States Public Health Service, promises to be the most illuminating investigation of its type yet undertaken. The material, culled in Alabama from 1,782 male Negroes aged 25 or more who were serologically examined, included 399 syphilitic Negro males who had never received treatment, and 201 presumably nonsyphilitic Negro males. The untreated group all gave a history of infection and each had at least two positive serologic tests for syphilis. The first paper (*30*) presents a comparison between the morbidity rate in the untreated syphilitic patients and that observed in the nonsyphilitic Negroes. In the first group there were 46.6 percent with evidence of circulatory disease, as compared with 23.9 percent in the nonsyphilitic group. Also, 26.1 percent of the untreated syphilitic Negroes had either clinical or serologic evidence of central nervous system abnormalities, while only 2.5 percent of the nonsyphilitic group had any disease of this system. Finally, 12.5 percent of the untreated patients with syphilis presented evidence of disease of the bones, joints, and bursae. Information as to the duration of the disease in these patients at the time of their inclusion in the study is not given, but good evidence is presented to warrant the conclusion that morbidity in the untreated male Negroes with syphilis far exceeded that in a comparable presumably nonsyphilitic group.

These studies were extended in a later communication (*36*) dealing with the effect of the disease on the life span of the human host. The material on which this report was based was expanded to include 410 Negro men with untreated syphilis, in addition to the previously described group of 201 uninfected Negro men. Careful follow-up infor-

mation regarding these individuals was obtained since their original selection in the winters of 1931–32 and 1932–33, and it was felt that not one individual still living had been completely lost from observation. Through the end of 1944, 129 were known to have died, and 93 of these were examined post mortem. The study as reported was limited to the 12-year period between January 1, 1933, and December 31, 1944. Of the original group of 410 syphilitics, 101, or 24.6 percent, had died, as contrasted with only 28, or 13.9 percent, of the 201 controls. Life tables for the 2 groups were constructed and it was concluded that the life expectancy of the Negro man of age 25 to 50, infected with syphilis but untreated, was reduced on the average by about 20 percent. This investigation is still in progress, and subsequent publications dealing with the life cycle of the untreated disease, supplemented by the detailed post-mortem examinations that were conducted, will without doubt comprise an outstanding contribution to the literature, equaling if not exceeding in importance, the work of Bruusgaard.

These two studies employ different technics in their approach to the identical problem. Bruusgaard conducted clinical examinations on living patients, and surveyed the death records of deceased patients, all of whom at varying periods before had been classified as having early syphilis, and none of whom had received modern antisyphilitic therapy. The United States Public Health Service group is conducting continuing clinical studies, including autopsy investigations, on a carefully selected group of untreated early syphilis patients, information on whom can be expected to cumulate with the passage of time. The present report utilizes a third technic, heretofore not employed. All cases with historical, laboratory, or morphologic evidence of syphilis were selected from a large autopsy series, which has been described in previous chapters. The clinical record of each of these patients was reviewed and classified according to the kinds and amounts of therapy. The group of syphilitic patients for whom no evidence of therapy could be found is described in the present communication. This, then, is a retrospective study, and similar in this regard to the work of Bruusgaard. However, since the group was culled originally from an autopsy population, each individual in it was studied by post-mortem examination.

Material

The 380 patients with syphilis who constitute the basic material of this series of reports are classified in table 37 according to their treatment status. Of this entire group, 198 patients received no treatment for their disease with the following 11 exceptions: 4 received 2 bismuth injections, 3 received 3 bismuth injections, 2 received 4 bismuth injections, 1 received 5 bismuth injections, and 1 received mercury inunctions and potassium iodide by mouth for 6 weeks. All of these patients were considered to have been untreated, and are so classified in the subsequent analysis. There were 129 males and 69 females in this group of untreated syphilitic patients. The large majority, 150, were white and the remaining 48 were Negroes. At autopsy the central nervous system of 116 or 58.6 percent was examined.

TABLE 37.—*Treatment status of 380 syphilitic patients*

Treatment	Cases					
	No.	Percent	No.	Percent	No.	Percent
Untreated	198	70.2	198	66.2	198	52.1
Inadequately treated[1]	72	25.5	72	24.1	72	18.9
Adequately treated[2]	12	4.3	12	4.0	12	3.2
Total	282	100.0	.....	.....	.....	.....
Treated but type and amount not known	.....	.....	17	5.7	17	4.5
Total	.....	.....	299	100.0	.....	.....
Unknown	.....	.....	.....	.....	81	21.3
Total	.....	.....	.....	.....	380	100.0

[1] Less than 20 arsenical and 20 heavy-metal injections
[2] 20 or more arsenical and 20 or more heavy-metal injections.

It is evident from table 37 that in the period under review from 1917 to 1941, a majority of patients with syphilis who died and were autopsied at the New Haven Hospital received no treatment for their disease. Of those whose treatment status was known, about three-quarters never were treated, while only from 3 to 4 percent of the entire group received adequate amounts of therapy according to accepted standards prior to the introduction of rapid treatment methods or of penicillin.

The duration of infection could be determined from the hospital records in only 37 of the 198 cases. Of these, 18 were known to have been infected for from 1 to 20 years, and 19 for from 21 to 30 or more years. Because of the relatively scant information available on this aspect of the study, it is not possible to ascertain whether the time when infection occurred was in any way related to the absence of treatment. In table 38 is shown the year of death and autopsy of the 198 patients. A large majority, 71.2 percent of the total, were autopsied in 1927 or later, that is, 17 or more years after the discovery of arsphenamine. Thus a considerable but unknown number of the group probably acquired infections in the postarsphenamine period.

TABLE 38.—*Year of death and autopsy of 198 untreated syphilitic patients*

Year	Patients	
	Number	Percent
1917–21	29	14.7
1922–26	28	14.1
1927–31	43	21.7
1932–36	53	26.8
1937–41	45	22.7
Total	198	100.0

In table 39 are recorded the criteria for the diagnosis of syphilis in the 198 untreated patients. Comparable values for the basic group of 380 patients also are shown. This classification is roughly arranged in decreasing order of clinical certainty of diagnosis. By positive anamnesis is meant a history of infection, or a history of treatment of an infection, or a known previously positive serologic test for syphilis (STS) at some other clinic. In the final category of the table are placed a small number of patients never clinically diagnosed as syphilitic, but included because of the presence of specific anatomic changes at autopsy. The first three classes encompass 85 percent of the total untreated group, the diagnosis of syphilis in these patients having been based on historical evidence of infection together with a positive STS or spinal fluid, or significant lesions at autopsy.

Results

Table 40 summarizes the final status of the 198 untreated cases. Only 77 of this number, or 38.9 percent, presented any anatomic changes at autopsy consistent with a diagnosis of syphilis. In not all of these patients, however, was syphilis the primary cause of death. In less than half of those (31 patients, or 15.7 percent of the total) showing syphilitic lesions at autopsy, death occurred primarily as a result of some other disease. The majority of the 198 patients (121, or 61.1 percent) presented no evidence at autopsy of tissue alterations suggestive of syphilitic disease. In 80 of these, or 40.4 percent of the entire group, the serologic test for syphilis during the last hospital admission was positive, and 35 patients, or 17.7 percent of the total, had a negative STS on their last admission to the hospital. A final group of 6 patients with no anatomic evidence of syphilis had a doubtful or unknown STS.

TABLE 39.—*Criteria for diagnosis of syphilis in 198 untreated patients*

Description	Total cases		Untreated cases		Treated cases	
	Number	Percent	Number	Percent	Number	Percent
1. Positive anamnesis, positive STS or spinal fluid on last admission	213	56.1	127	64.1	86	47.3
2. Positive anamnesis, positive STS on previous admission	43	11.3	10	5.1	33	18.1
3. Positive anamnesis, no serologic or clinical evidence of syphilis on last admission but confirmation at autopsy by positive STS or presence of anatomic lesions	57	15.0	31	15.7	26	14.3
4. Positive anamnesis but doubtful STS on last admission	3	.8	1	.5	2	1.1
5. Positive anamnesis but no STS on last admission	15	3.9	5	2.5	10	5.5
6. Positive anamnesis but negative STS on last admission	38	10.0	23	11.6	15	8.2
7. Negative anamnesis, no STS on last admission, but anatomic lesions present at autopsy	11	2.9	1	.5	10	5.5
Total	380	100.0	198	100.0	182	100.0

TABLE 40.—*End results in 198 untreated syphilitic patients*

End result	Number		Percent	
Anatomic lesions present	77		38.9	
Primary cause of death		46		23.2
Subsidiary findings		31		15.7
Anatomic lesions absent	121		61.1	
STS positive		80		40.4
STS negative		35		17.7
STS doubtful or not known		6		3.0
Total	198	198	100.0	100.0

The anatomic lesions encountered at autopsy in the 77 patients with anatomic changes are tabulated in table 41. Of the 46 patients whose deaths were directly the result of syphilitic changes, 27 presented only one of the diagnostic categories listed in the table, 13 had two of these organic changes, and 6 had 3, with a total of 71 different recognizable syphilitic lesions. Of the 31 patients who died of some other disease process, but who had syphilitic lesions unrelated to the primary cause of death, 27 showed a single specific lesion, and 4 presented evidence of two different lesions. None in this group had three of the changes shown in table 41.

Discussion

A comparison of the Yale material with that reported by Bruusgaard shows a remarkable similarity between the two (table 42). About 39 percent of our group of untreated syphilitic patients were found at autopsy to have anatomic evidence of syphilis, as contrasted with Bruusgaard's finding of 35 percent with clinical or post-mortem organic lesions of syphilis. In the Yale series 23 percent died primarily as a result of syphilitic disease and Bruusgaard's population included an identical ratio, 23 percent, with one or another of the serious end results of syphilis. Conversely, in the Yale series 61 percent died with no anatomic evidence of syphilis, while Bruusgaard's group included 65 percent who were living or who had died without any indication of organic syphilis. The ratio of positive and negative serologic results in the two groups is somewhat different, but this perhaps may be accounted for by two factors: (1) The large group in Bruusgaard's series whose STS was not known, and (2) the differences which no doubt existed in the

TABLE 41.—*Anatomic findings in 77 patients with untreated syphilis among whom 106 lesions were found at autopsy*

Type of lesion	Number of lesions found—			
	In 46 patients dying primarily of syphilis	In 31 patients with syphilitic changes a subsidiary finding	In all 77 patients	
			Number	Percent
Cardiovascular:				
Aortitis with or without valvulitis	26	29	55	
Aneurysm of arch	8	1	9	
Aneurysm of abdominal aorta	1	2	3	
Coronary arteritis	4	0	4	
Aortitis of leg vessels	3	0	3	
Cerebral arteritis	2	0	2	
Ruptured aneurysm of arch	9	0	9	
Ruptured aneurysm of innominate artery	1	0	1	
Ruptured cerebral aneurysm	2	0	2	
All cardiovascular	56	32	88	83.0
Central nervous system:				
Tabes	2	1	3	
Meningitis	2	0	2	
Cerebral neurosyphilis	2	0	2	
Optic atrophy	0	1	1	
Total central nervous system	6	2	8	7.6
Other types:				
Gumma of brain	1	0	1	
Gumma of heart	1	0	1	
Gumma of liver	3	0	3	
Gumma of testis	0	1	1	
Gumma of meninges	3	0	3	
Cirrhosis of liver	1	0	1	
Total other types	9	1	10	9.4
Grand total	71	35	106	100.0

TABLE 42.—*Summated comparison of end results of untreated syphilis in Bruusgaard's and the Yale series*

	Bruusgaard		Yale	
	Number	Percent	Number	Percent
Organic syphilitic disease	166	35.1	77	38.9
No evidence of syphilis, STS+	68	14.4	80	40.4
No evidence of syphilis, STS—	132	27.9	35	17.7
No evidence of syphilis, STS not known	107	22.6	6	3.0
Total	473	100.0	198	100.0

sensitivity of the serologic tests employed in the two series.

From table 41 it is seen that only about 8 percent of the Yale group presented any evidence of syphilitic disease of the central nervous system. A post-mortem examination of the central nervous system is not a routine procedure in our laboratory. If it were, perhaps a larger number of patients with central nervous system involvement might have been found, and this in turn would have increased the proportion of poor end results. This possibility cannot of course be dismissed lightly. However, there are two factors that should be considered. In the first place it has been a practice to make special efforts to obtain permission for an examination of the central nervous system whenever clinical signs suggest involvement of this system. Furthermore, as shown in table 43, of 116 patients whose autopsy examination included a study of the central nervous system, 47, or 40.5 percent, had anatomic evidence of syphilitic disease. This value does not differ significantly from the 36.6 percent of the 82 patients who did not have post-mortem examinations of the central nervous system but who did show anatomic lesions of other organs. The two groups show no evidence of heterogeneity with respect to the presence or absence of anatomic lesions and this suggests that the failure to examine the central nervous system in all cases may not have materially influenced the result.

Sowder has shown that Bruusgaard's data are weighted to emphasize the more serious complications of the disease. The Yale material may be subject to the opposite criticism that, particularly as regards central nervous system syphilis, it is weighted in favor of the less serious end results of syphilis. The New Haven Hospital, a general hospital for acute diseases does not make a practice of admitting the deteriorated patient with central nervous system syphilis. These patients ultimately reach the various State hospitals, and to this extent our material is biased. We have no method of evaluating the influence of this sampling error on our end results, but the general agreement between our findings and those of Bruusgaard suggests that it is not excessive.

If it is assumed that our findings represent a fairly accurate summary of the end results of untreated syphilis, it can be concluded that had treatment been administered adequately and early to the entire group it could not possibly have effectively altered the course of the disease in more than 4 out of 10 patients, since 6 out of 10 untreated patients died with no evidence of syphilis at autopsy. On closer inspection even this ratio of 4 out of 10 patients who could have benefited by treatment is excessive, because only a little more than 2 out of 10 actually died as a result of syphilis. The remaining 8 out of 10 patients with syphilis all succumbed to an unrelated disease process, and the fact that some of them had developed a syphilitic lesion, or a positive STS, was apparently of no great significance. Treatment of the whole group could then have possibly altered the

TABLE 43.—*Presence or absence of anatomic lesions of syphilis in patients with and without post-mortem examination of central nervous system*

	C. N. S examined		C. N. S not examined		Total	
	Number	Percent	Number	Percent	Number	Percent
Anatomic lesions present	47	40.5	30	36.6	77	38.9
Anatomic lesions absent	69	59.5	52	63.4	121	61.1
Total	116	100.0	82	100.0	198	100.0

end result in only the 2 who actually died of syphilis out of 10 untreated cases.

This conclusion, however, does not place proper emphasis on the fact that syphilis is a dynamic disease, static at some times, progressive and developing at others. Certainly an unknown number of the group with incidental syphilitic lesions at autopsy would have died of syphilis had they survived the illness to which they finally succumbed. Some of these syphilitic lesions, if given time to develop, would have progressed to a stage where death would have resulted. Furthermore, the real significance of a positive STS in the absence of anatomic lesions is not fully understood. No doubt the serologic findings in some of these instances reflect the immune state of the host, but in others it may very well represent the reaction to tissue changes unrecognizable by known technics. Insofar as the latter hypothesis is correct, a positive STS may indicate an early phase of a reactive process which, provided the patient lives long enough, ultimately develops into a recognizable anatomic lesion. The value of antisyphilitic treatment should therefore not be gaged in the limited terms of the 2 out of 10 in the Yale group who died of syphilis. Rather is the value of syphilis therapy directly related to the over-all efforts to prolong life by reducing the mortality from other diseases. Every syphilitic patient saved by sulfonamide preparations or penicillin from death due to pneumonia, or appendiceal abscess, or meningitis, or streptococcic infections, becomes liable to death from syphilis. Every syphilitic patient with malignant disease, or traumatic injuries, or hypertension who is cured by surgical intervention becomes ultimately susceptible to death from syphilis. Viewed in this light the prompt and adequate treatment of patients with syphilis becomes a life-saving measure out of all proportion to the 2 in 10 ratio which in this study was the actual death rate from untreated syphilis.

The above statements have emphasized mortality as a direct result of syphilitic infection and have failed to give proper weight to the influence of syphilis on host susceptibility to other diseases. Definitive information on this point is not available, but a preliminary study of the autopsy data from Alabama (37) gives the impression that the great difference in mortality rates between the syphilitic and control groups in that investigation was due as much to other diseases as to syphilis itself. This suggests that many may have succumbed to an intercurrent disease more easily because of syphilitic infection. This impression is corroborated by the recent study of Deibert and M. C. Bruyere (38), which shows that there is greater morbidity present among untreated syphilitics than among nonsyphilitics, even in areas not commonly associated with syphilis. It is apparent that a case fatality rate of at least 20 percent is ample justification for the most strenuous efforts to provide prompt and adequate treatment of all cases. This is the more true since fatalities due to syphilis usually follow long periods of disability. Even when not fatal, there is evidence to suggest that syphilis probably lowers life expectancy significantly.

Nevertheless the evidence at hand does indicate that syphilis is occasionally a self-limited disease. In the Yale material there were 35 patients (17.7 percent of the total syphilitic group) with a negative STS during their last hospital stay, and with complete absence of anatomic evidence of syphilis at autopsy. From all indications these patients were spontaneously cured, demonstrating that a certain proportion of individuals possess adequate defense mechanisms which can counteract syphilitic infection and completely eliminate any morphologic evidence of the disease. The exact nature of these defense factors is not known but their sum total is encompassed in the general term "host resistance." The recognition that host resistance to syphilis does exist should serve as an impetus to studies in this field.

CHAPTER 9

RÉSUMÉ AND RECOMMENDATIONS

A review of the available literature on the incidence of morphologic evidence of syphilis in autopsies on adults revealed widely different rates, varying from a low of 2.6 percent to a high of 29.5 percent. The factors which might have contributed to these different results were subjected to critical analysis. On the basis of these reports, it was established that lesions of syphilis were more frequently observed in the Negro race than in the white, and that they were likewise more frequent in males than in females, but it could not be demonstrated conclusively that these factors were responsible for the divergent estimates of the incidence of syphilis at autopsy. The great variability in diagnostic criteria, both gross and microscopic, employed by different investigators was appraised, and it was concluded that it was this lack of uniformity in diagnostic criteria which was the major factor responsible for the widely diverse findings reported in the literature.

These observations initiated a survey of the Yale material, which had as its purpose the study of many of the problems not heretofore clarified in reports on syphilis at autopsy. From September 22, 1917, to March 8, 1941, 5,300 autopsies were performed at the Yale University School of Medicine. Of these 3,907 were upon individuals aged 20 or over, and of this number, 380, or 9.7 percent, had clinical or laboratory or postmortem evidence of syphilis. The method employed in selecting two control groups from the nonsyphilitic population for further comparison with this syphilitic group was described, and it was demonstrated that these two control groups represent random samples from the total nonsyphilitic population as regards age, sex, and race. The punch-card code which was utilized in all subsequent analyses of this material was also presented.

The highest rates for syphilis at autopsy were reported by investigators who accepted Warthin's criteria of fibrosis and round cell infiltration for the morphologic diagnosis of syphilis. The lowest rates, on the other hand, were observed by those who either antedated Warthin or did not adopt his teachings. Clearly here was a problem which could be clarified by a study of the Yale material. To accomplish this purpose, microscopic preparations of the heart, liver, pancreas, adrenals, and testes from 283 syphilitic and 722 nonsyphilitic white persons were studied with respect to the frequency of Warthin lesions. No qualitative differences could be discerned between the fibroid and cellular changes observed in the organs of syphilitic persons and those of the nonsyphilitic controls. The two groups did not differ significantly when they were compared with respect to the incidence of Warthin lesions in the heart, liver, adrenals, and testes. Pancreatic lesions were probably significantly more frequent among syphilitics than among nonsyphilitic persons, but no explanation could be found for the relatively high frequency of these changes in the latter group. The group of syphilitic persons was divided into two categories, those with and those without frank anatomic alterations characteristic of syphilitic infection, and the incidence of Warthin lesions of the five parenchymatous organs in the two subgroups was compared. In no instance was a significant difference found. Finally an analysis of the age distribution of persons with and without Warthin changes indicated that the aging process is related to the presence of these lesions. On the basis of these findings it was concluded that the evidence did not support the concept that the microscopic changes described by Warthin are pathognomonic of syphilitic infection.

The Yale autopsy material was studied for information on morbidity and mortality rates and the variables affecting these rates. Of the

3,907 individuals over 20 years of age who were autopsied in the period under review, 380 had clinical or laboratory or anatomic evidence of syphilis. This represents 9.7 percent of the population, and confirms the statement that "syphilis strikes 1 out of 10 adults." In this group of syphilitics were 156 individuals, or 41 percent, with morphologic lesions of syphilis, and 90, or 57.7 percent, of these died primarily as a result of their syphilis. In this experience 3 out of 10 persons with clinically diagnosed syphilis developed significant tissue lesions, and 1 out of 5 died therefrom. A summation of three different autopsy populations, one of which was the Yale material, disclosed that syphilitic lesions at autopsy were from two to four times as frequent in the Negro as in the white. Nevertheless, the syphilitic Negro appeared no more likely to develop a tissue lesion recognizable at autopsy and had no greater chance of dying therefrom than the white syphilitic. The mean age at death of syphilitic and nonsyphilitic Negroes was identical, but both of these groups died at a significantly earlier mean age than whites of comparable categories. This observation suggests that the shorter life expectancy of Negroes as contrasted to whites may be due not to the greater frequency of syphilis among Negroes, but rather to nonspecific social and economic influences which adversely affect their life span.

In the Yale series, syphilitic males with lesions at autopsy comprised 4.7 percent of the male population and syphilitic females with lesions constituted 2.7 percent of the female population. These two values are significantly different. Sex, therefore, appeared to exert a definite influence on resistance to the tissue changes of late syphilis, and this was independent of race.

In a consideration of the white individuals examined at autopsy in the Yale series, no significant differences were found among the mean ages at death of any of the following groups: Nonsyphilitic controls, syphilitics with anatomic lesions, syphilitics without anatomic lesions, syphilitics dying primarily of the disease, syphilitics with anatomic lesions of syphilis who died of an unrelated disease process. All of these groups had a mean age at death of approximately 53 years. However, a significantly higher percentage of deaths occurred among syphilitics in the age group 40 to 70 years than among nonsyphilitics. Moreover, although about 20 percent of nonsyphilitics survived age 70, only about 10 percent of syphilitics survived this age. This was true not only for the syphilitics with lesions at autopsy, but also for those without anatomic lesions. From these findings the conclusion was reached that the mere fact of syphilitic infection significantly reduces longevity, regardless of whether or not tissue lesions result.

Of the 380 syphilitics comprising the Yale material, 197 had positive and 116 negative serologic tests on their last hospital admission. A study of this combined group of 313 cases resulted in the following conclusions:

1. Serologic positivity was significantly more frequently associated with anatomic lesions than was serologic negativity.

2. Approximately one-quarter of all syphilitics with specific anatomic lesions at autopsy were serologically negative on their last admission.

3. Approximately one-half of all individuals with positive serologic tests showed no anatomic changes consistent with a diagnosis of syphilis at autopsy.

4. In patients with positive serologic tests, the presence of anatomic lesions was diagnosed correctly in about three-fourths of the cases. About one-fifth of all patients with positive tests as the only indication of infection had organic lesions of syphilis at autopsy, and syphilis was primarily responsible for the death of 1 in 20.

5. In syphilitic individuals with negative serologic tests, a clinical evaluation leading to a specifically stated impression of "no anatomic lesion" or "cured" was likely to be no more accurate when checked with findings at autopsy than a clinical diagnosis of organic disease.

6. About four-fifths of the syphilitics who died primarily as the result of organic syphilitic disease had positive serologic tests. The frequency of positive tests in this group was greater than in the group with anatomic lesions of syphilis an incidental finding at autopsy,

while the group with no lesions at autopsy had the lowest proportion of positive tests. This suggests that increasing activity of the disease is associated with an increasing frequency of positive blood tests.

7. Syphilitic organic disease was primarily responsible for the death of about one-quarter of all cases with positive and about one-tenth of those with negative serologic tests. The likelihood of syphilis being the primary cause of death was more than twice as great in individuals with positive as in syphilitics with negative serologic tests.

8. Anatomic changes of syphilis were observed in about one-sixth of those in whom serologic reversal had occurred.

9. Sex did not influence the incidence of positive or negative serologic tests among individuals with syphilitic lesions at autopsy or the frequency of syphilitic lesions as a primary cause of death.

In view of Warthin's reports on the tissue changes which he interpreted as pathognomonic of syphilitic infection, the relation of these lesions to the results of serologic tests for syphilis was investigated. Two groups of syphilitic individuals, one group with positive and the other with negative serums, were compared as to the frequency of the Warthin changes in each of five parenchymatous organs. Organ for organ, the incidence of these lesions in the two groups was not significantly different. Moreover, syphilitic persons with typical Warthin lesions in multiple organs were no more likely to present serologic evidence of syphilis than were those with Warthin lesions in only one organ. On the basis of these findings, it was concluded that the changes described by Warthin are not related to the reaction of the serum to known tests for syphilis.

Of the 380 syphilitic patients who are described in this series of reports, 198, or 52.1 percent, received no specific therapy. A study of this group was made in order to determine the distribution of morphologic lesions of syphilis in an untreated syphilitic population. Anatomic lesions of syphilis were found in 77, or 38.9 percent, of these untreated patients, but only 23.2 percent of the entire group died primarily as a result of syphilis. One hundred and six different lesions were found in these 77 syphilitics; 88 (83.0 percent) occurring in the cardiovascular system, and 8 (7.6 percent) occurring in the central nervous system. The remainder (10, or 9.4 percent) were gummatous lesions of various organs, and cirrhosis of the liver. Anatomic lesions of syphilis were absent in 121 patients (61.1 percent). In 80 (40.4 percent), the blood serologic test during the last hospital stay was positive, and in 35 (17.7 percent) it was negative. From these findings it appears that untreated syphilis in this series had a case fatality rate of about 1 in 5, and a spontaneous cure rate also of about 1 in 5. There was a close parallelism between these observations and those reported by Bruusgaard.

Recommendations

With the completion of this series of reports, it is apparent that two serious deficiencies must be overcome if future studies of a similar nature are to prove worth while.

Anatomic Criteria for Diagnosis of Syphilis

The first chapter has emphasized the widely different criteria employed in different laboratories of pathology for the anatomic diagnosis of syphilis. Until uniform criteria are generally adopted and consistently followed in the large teaching centers, it is improbable that any definitive understanding of the anatomy of the disease syphilis will result. In order to overcome this obstacle to a comprehension of the basic disease process, it is suggested that a committee of pathologists be organized under the auspices of the United States Public Health Service to consider the entire question of the morphologic criteria for a diagnosis of syphilis. Such a committee should be aided by the establishment of a registry of anatomic syphilis, to which pathologists from all over the country would be invited to contribute material for diagnosis and study. On the basis of continuing studies, the committee would present its conclusions in a series of authoritative and comprehensive recommendations. These would no doubt be

readily accepted by the profession in general and by pathologists in particular. Thus one of the pitfalls to our understanding of the disease would be eliminated.

Inadequacy of Sample

Autopsies conducted over a period of a quarter of a century at the Yale School of Medicine produced only a handful of syphilis cases, 380 in number, for study in these reports. Again and again, as indicated in the text, this group proved to be an inadequate sample from which to draw conclusions. At least two important originally contemplated studies were of necessity abandoned because of the inadequacy of our sample. These were: (1) an evaluation of the influence of syphilis on host susceptibility or resistance to other disease processes, and (2) a survey of the end results of adequately treated syphilis. Neither of these subjects has to date been studied on the basis of autopsy material. If the autopsy protocols of other institutions were pooled with our own, a reservoir of information would soon be available from which would flow many of the answers to the vexing questions posed in the body of these reports. Such a cooperative enterprise could be formally organized under the auspices of the United States Public Health Service. The pattern of procedure utilized with such success by the Penicillin Panel of the National Research Council in studying the effectiveness of penicillin in the treatment of syphilis could readily be utilized. This proposal envisages the organization of a Central Statistical Bureau for the coding and punch carding of autopsy protocols submitted by participating institutions. In this manner a mass of data would soon become available which could serve as the basis for the investigation not only of syphilis, but also of many other morbid processes.

APPENDIX

Code for Syphilis Survey

Column	*Description*
1–4	Autopsy number
5–6	Year of autopsy
7–8	Month of death
9–10	Type of autopsy 1 Thorax 2 Abdomen 4 Head 8 Spinal cord 16 Neck organs 32 Extremities (Code sum)
11	Hospital and service 1 New Haven—Medical 2 New Haven—Surgical 3 New Haven—Maternity—mother 4 New Haven—Maternity—infant 5 New Haven—Other 6 Outside doctor—No hospital admission 7 Outside tuberculosis hospital 8 Outside—Other than tuberculosis hospital 9 Medical examiner or coroner (in or out hospital) 0 Sudden death
12	Reserved for expansion
13	Clinical status last admission 0 Cured—Negative Wassermann and no clinical evidence 1 Latent—Only evidence is positive Wassermann 2 Cardiovascular syphilis 3 Central nervous system syphilis 4 Cardiovascular plus central nervous system 5 Other than cardiovascular or central nervous system 6 Cardiovascular plus other than central nervous system 7 Central nervous system plus other than cardiovascular 8 Cardiovascular plus central nervous system plus other 9 No serological or clinical evidence of syphilis, but positive past history overlooked on last admission
14–15	Age in years—Age known Code years
16	Age in years—Age not known but estimated 2—20 to 29 years 3—30 to 39 years 4—40 to 49 years 5—50 to 59 years 6—60 to 69 years 7—70 to 79 years 8—80+
17	Sex 1 male 2 female 3 not known
18	Marital status 1 unmarried 2 marital status unknown 3 married, widower, or divorced (males only) 4 married, nulliparous 5 married, parous 6 married, gravidity unknown
19	Nativity 0 United States 1 England, Ireland, Scotland, and Wales 2 Europe, except Russia and Slavs and Scandinavians 3 Russia and Slavs (Jugo, Czechs, Poland, Bulgaria) 4 Scandinavia 5 Latin America, South America 6 Asiatic 7 All others 8 Unknown
20	Color 0 unknown 1 white 2 black 3 yellow 4 all others
21	Occupation 0 unknown 1 housewife 2 laborer unclassified 3 trades 4 personal service and clerical 5 transportation 6 profession and skilled trades 7 all other employed 8 school 9 unemployed (includes women)

Column	*Description*
22	History of early syphilis—Personal 0 no history or unknown 1 primary genital lesion 2 primary extragenital lesion 3 secondary 4 primary and secondary
23	History of late syphilis 0 unknown or no history 1 cardiovascular 2 central nervous system 4 other, including positive serology (Punch sum)
24	History of syphilis, familial 0 unknown or no history 1 spouse with syphilis 2 offspring with syphilis 4 siblings with syphilis (Punch sum)
25	Diagnosis of syphilis 1 ante mortem 2 post mortem 3 ante mortem and post mortem 4 not diagnosed either ante or post mortem
26	Diseases diagnosed ante mortem 1 diabetes 2 Buerger's disease (Punch sum)
27	Serology—Ante-mortem Wassermann, alcohol, or cholesterol antigen 0 unknown or not done 1 negative } Last admission 2 doubtful } Last admission 3 positive } Last admission 4 previously positive but negative on last admission (± or + = doubtful. If two tests are performed, err in favor of positivity.)
28	Serology—Ante-mortem Kahn Same as column 27
29	Serology—Ante mortem, other than Kahn or Wassermann Same as column 27
30	Serology—Post mortem, any test Same as column 27
31–32	Spinal Fluid 00 unknown or not done 0 all negative 1 abnormal sugar—below 45 or above 85 2 abnormal protein—more than 45 4 increased w. b. c.—more than 8 8 r. b. c. present 16 serology positive 32 colloidal gold—abnormal (Punch sum)
33	Darkfield examination 0 performed but results not known 1 not done 2 negative and doubtful 3 positive
34	Blood pressure—systolic 0—not known 1—under 99 2—100–139 3—140–199 4—over 200
35	Blood pressure—diastolic 0—not known 1—under 50 2—under 75 3—75–99 4—100–124 5—over 125
36	Duration of disease 0—less than 1 year 1—1 to 5 years 2—6 to 10 years 3—11 to 15 years 4—16 to 20 years 5—21 to 25 years 6—26 to 30 years 7—over 30 years 8—unknown
37	Treatment—Arsenical (trivalent) 0—unknown 1—no treatment 2—less than 10 injections 3—10 to 19 injections 4—20 or more 5—received, but number not known
38	Spacing of treatment—arsenical 0 not known 1 continuous 2 discontinuous
39	Stage of disease at first arsenical 0 unknown 1 seronegative primary 2 seropositive primary 3 sero-unknown primary 4 secondary 5 latent syphilis (after 2 years) 6 tertiary (with lesion)

Column	Description
40	Treatment—Heavy metal Same as column 37
41	Stage of disease at first heavy metal Same as column 39
42–43	Other treatment 1 treatment given but character or amount unknown 2 tryparsamide 4 hyperpyrexia 8 other (Punch sum)
44	Post-mortem diagnosis of syphilis 1 gross with no microscopic confirmation 2 gross with microscopic confirmation 3 microscopic with no gross confirmation
45	Microscopic fibrosis and/or round cells in testicle 0 slide absent 1 no increased fibrosis or round cells 2 minimal, 3 intermediate, 4 maximal: fibrosis of interstitium and round cells plus tubular atrophy 5 — 6 — 7 — 8 other pathological process obscuring picture
46	Microscopic fibrosis and/or round cells in liver 0 slide absent 1 minimal, 2 intermediate, 3 maximal: fibrosis with round cell infiltration 4 no increased fibrosis but round cells present 5 no fibrosis and no round cells 6 other pathological process obscuring picture
47	Microscopic fibrosis and/or round cells in pancreas Same as column 46
48	Microscopic fibrosis and/or round cells in adrenal 0 slide absent 1 no increase in fibrosis or round cells 2 minimal, 3 intermediate, 4 maximal: round cells without fibrosis 5 — 6 — 7 —
49	Microscopic fibrosis and/or round cells in heart 0 slide absent 1 no increase in fibrosis and no round cells 2 minimal, 3 intermediate, 4 maximal: fibrosis with round cell infiltration 5 — 6 — 7 — 8 other pathological process obscuring picture
50–51	Heart weight in decigrams 00 no weight or not recorded
52	Coronary arteries 0 not examined or unknown 1 essentially normal 2 narrowed moderately 3 narrowed markedly 4 occluded
53–54	Treatment reaction 1 dermatitis 2 purpura 4 encephalitis 8 jaundice 16 aplastic anemia 32 any other (Punch sum)
55	Experimental or control group 1 experimental 2 control group A 3 control group B
56	Number of cards for case
57–58	Reserved for expansion
59	Syphilis at autopsy 1 syphilis primary cause of death 2 syphilis incidental finding 3 syphilis not evident at autopsy
60	Other anatomical findings 1 disease of gallbladder 2 disease of prostate 4 disease of fallopian tubes (Code sum)
61–67	Principal primary autopsy diagnosis (Primary cause of death)
68–74	Subsidiary disease process at autopsy
75–78	Syphilis at autopsy
79	Reserved for expansion
80	Card number of case

REFERENCES

1. MOORE, J. E.: Unsolved clinical problems of syphilology. Am. J. Syph., Gonor. & Ven. Dis., 23: 701, 1939.

2. BRINES, O. A.: Laboratory diagnosis of syphilis. *In* papers of the Michigan Academy of Science, Arts and Letters, Ann Arbor, Mich., University of Michigan Press, 21: 561, 1936.

3. TURNBULL, H. M.: Alterations in arterial structure and their relation to syphilis. Quart. J. Med., 8: 201, 1914–15.

4. POHLEN, K.: Ueber die Häufigkeit der Syphilis und der syphilitischen Folgezustände nach dem klinischen und pathologischen Gefund. Dermat. Wchnschr. 105: 1469, 1937.

5. WARTHIN, A. S.: The new pathology of syphilis. Am. J. Syph., 2: 425, 1918. The role of syphilis in the etiology of angina pectoris, coronary arteriosclerosis and thrombosis, and of sudden cardiac death. Am. Heart J., 6: 163–170, 1930.

6. HALA, W. W.: Incidence of syphilis. An analysis of 1088 autopsies. Am. J. Syph., 6: 616, 1922.

7. OPHÜLS, W.: A statistical survey of three thousand autopsies. Stanford University Pub., Univ. Series, M. Sc., 1: 234, 1926.

8. MANOHAR, K. D.: Incidence of syphilis. Indian J. Ven. Dis., 1: 9, 1935.

9. KOPPISCH, E.: La sifilis en Puerto Rico; Estudio basado en la revision de 1,000 autopsias consecutivas (informe preliminas). Bol. Asoc. Méd. de Puerto Rico, 31; 160, 1939.

10. BELL, E. T.: Frequency with which syphilitic lesions are encountered in post-mortem examinations. Arch. Path., 26: 839, 1938.

11. SYMMERS, D.: Anatomic lesions in late acquired syphilis. A study of 314 cases based on the analysis of 4,880 necropsies at Bellevue Hospital. J. A. M. A., 66: 1457, 1916.

12. OGDEN, M. A.: Aneurysm of the aorta. A clinicopathological analysis of 127 necropsies. Urol. & Cutan. Rev., 44: 731–735, 1940.

13. KEIDEL, A.; MOORE, J. E.: The Wassermann reaction in the Johns Hopkins Hospital. Bull. Johns Hopkins Hosp., 34: 16, 1923.

14. VONDERLEHR, R. A.; USILTON, L. J.: Syphilis among men of draft age in the United States. Analysis of 1,895,778 serologic reports of men aged 21–35 who were examined under the Selective Training and Service Act of 1940. J. A. M. A., 120: 1369–1372, 1942.

15. TURNER, T. B.: The race and sex distribution of the lesions of syphilis in ten thousand cases. Bull. Johns Hopkins Hosp., 46: 159, 1930.

16. PAULLIN, J. E.; DAVISON, H. M.; WOOD, R. H.: The incidence of syphilitic infection among the Negroes in the South. Its influence in the causation of disability, and the methods which are being used to combat the infection. Boston M. & S. J., 197: 345, 1927.

17. TEODORI, U.: Rilievi statistici concernenti la sifilide nel materiale autoptico del'Instituto di Anatomia Patologica di Firenze dal 1918 al 1935 con rilievi comparativi sulla frequenza dei tumori maligni e della tubercolosi. Dermosifilografo, 13: 143, 1938.

18. FRATES, A.: Considerazioni statistiche sulla sifilide nelle prime 10,000 autopsie del'Instituto di Anatomia Pathologica della r. Universita di Malano. Clin. Med. Ital., 65: 1015, 1934.

19. MELCHIOR, L.: Om sektionsfund og dodsaarsager hos patienter med erhvervet syfilis. Ugesk. f. laeger, 84: 1351, 1922.

20. SCHREK, R.: Further quantitative methods for the study of transplantable tumors: The growth of R39 sarcoma and Brown-Pearce carcinoma. Am. J. Cancer, 28: 345–363, 1936.

21. NICKEL, H.: Statistische Untersuchungen über die Haufigkeit der lues am Obductionsmaterial, Klin. Wchnschr. 15: 121–124, 1936.

22. WELLER, C. V.: The visceral pathology in Haitian treponematosis. Am. J. Syph., Gonor. & Ven. Dis., 21: 357, 1937.

23. GULDBERG, G.: Ueber Sektionsbefunde bei Syphilitikern. Arch. f. Dermat. u. Syph., 166: 730, 1932.

24. ROSAHN, P. D.: The punched card technique as applied to autopsy protocol analysis. J. Tech. Method. & Bull. Int. Asso. Med. Mus., 18: 32–36, 1938.

25. VONDERLEHR, R. A.; USILTON, L. J.: The chance of acquiring syphilis and the frequency of its disastrous outcome. Ven. Dis. Inform., 19: 396–404, 1938.

26. USILTON, L. J.; MINER, J. R.: A tentative death curve for acquired syphilis in white and colored males in the United States. Ven. Dis. Inform., 18: 231, 1937.

27. DUBLIN, L. I.: The problem of Negro health as revealed by vital statistics. J. Negro Education, 6: 268, 1937. (Quoted by H. H. Hazen in "Syphilis in the Negro," U. S. Publ. Health Service, Supp. No. 15 to Ven. Dis. Inform., 1942.)

28. SCHAMBERG, I. L.: The prognosis of syphilis Am. J. Syph., Gonor. & Ven. Dis., 29 529, 1945.

29. SMITH, D. C.; BRUYERE, M. C.: The effect of treated acquired syphilis on life expectancy. J. Ven. Dis. Inform., 27: 39-46, 1946.

30. VONDERLEHR, R. A.; CLARK, T.; WENGER, O. C.; HELLER, J. R., Jr.: Untreated syphilis in the male Negro. A comparative study of treated and untreated cases. Ven. Dis. Inform., 17: 260, 1936.

31. BRINES, O. A.: Serological diagnosis in histologically proved chronic syphilis. An analysis of 424 necropsies. J. Lab. and Clin. Med., 27: 15–19, 1941.

32. SCOTT, V.: Personal communication.

33. BRUUSGAARD, E.: The fate of syphilitics who are not given specific treatment. Arch. f. Derm. u. Syph., 157: 309, 1929.

34. MOORE, J. E.: The modern treatment of syphilis. 2nd ed. Springfield, Ill. Charles C. Thomas, 1943.

35. SOWDER, W. T.: An interpretation of Bruusgaard's paper on the fate of untreated syphilitics. Am. J. Syph., Gonor. & Ven. Dis., 24: 684-691, 1940.

36. HELLER, J. R., Jr.; BRUYERE, P. T.: Untreated syphilis in the male Negro. II. Mortality during 12 years of observation. J. Ven. Dis. Inform., 27: 34-38, 1946.

37. HELLER, J. R., JR.: Personal communication.

38. DEIBERT, A. V.; BRUYERE, M. C.: Untreated syphilis in the male Negro. III. Evidence of cardiovascular abnormalities and other forms of morbidity, J. Ven. Dis. Inform., 27: 301-314, 1946.

☆ U. S. GOVERNMENT PRINTING OFFICE: 1947— 747160

PAMPHLET BINDERS

This is No. 1527

also carried in stock in the following sizes

	HIGH		WIDE		THICKNESS
1523	9	inches	7	inches	½ inch
1524	10	"	7	"	"
1525	9	"	6	"	"
1526	9¾	"	7⅛	"	"
1527	10½	"	7½	"	"

	HIGH		WIDE		THICKNESS
1529	12	inches	10	inches	½ inch
1530	12	"	9⅛	"	"
1531	13	"	10	"	"
1532	14	"	11	"	"
1534	15	"	12	"	"